Complementary Medicines Australia submission to the TGA consultations; 'Proposed amendments to the Poisons Standard - Joint ACMS/ACCS meetings, June 2020':

2.5 Cannabidiol
2.2 Cannabidiol

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Executive Summary

Pharmacist Only access of very low dose cannabidiol will be not achieve the humanitarian goals of access and affordability sought by the recent Australian Senate Inquiry. In particular this is due to the lack of data at a low dose to pass the hurdle of product registration. It will likely take over a decade for sufficient products to be trialled, registered and sold at volumes that enable affordable access.

The market limitations of registration relative to the demand, and the resulting cost in comparison to the already extensive "illicit" community use of unregulated but well-tolerated cannabidiol, or homegrown cannabis of variable components, presents a regulatory scenario that will not be realistic to managing affordable access sought by the community, or furthering public health from the broader perspective.

Pharmacist Only access of low dose cannabidiol requiring registration will additionally bottle-neck research into other potentially effective medicinal cannabis preparations for more serious diseases, which may be supplied as prescription medicines if new efficacy data became available.

Cannabidiol has been recognised by the WHO as having a low chance of misuse. Removing a standardised cannabidiol preparation from the Poisons Standard as proposed by the private application [2.2], can be appropriately mitigated by controls proposed as part of the TGA's application [2.5] including the 1mg/kg/day limit, provided it matched to current ABS Australian health statistics.

The key safety concern of the TGA's review relates to drug interactions - the cytochrome P450 enzyme. We concur with the view that this is unlikely to occur to a physiologically or clinically relevant degree and are not aware of reports of drug interactions with low dose CBD (i.e. 1 mg/kg/day). The profile appears to be not any more significant than certain foods that are not managed with warning statements, or listed medicines (such as St John's Wort) which are effectively managed by label warnings. Unscheduled low dose access safety would be further ensured by any other requisite controls for manufacturing, labelling and claims in the post-Scheduling environment.

The most effective and affordable access will occur by inclusion of cannabidiol on the Permissible Ingredients Determination at the request of the Minister. Accompanied by a possible TGA Monograph for claims, and a requirement that it cannot be supplied in a medicine with other active ingredients for a period of 3-5 years, will ensure health effects and pharmacovigilance can be monitored efficiently.

In this way, CMA's 'hybrid' proposal applies multi-faceted controls for risk reduction whilst reaching the humanitarian objective sought by the Australian Senate which fundamentally underlies this review.

Although international controls differ, cannabidiol is seen to be widely available in other jurisdictions with variable regulation. Australian manufacturers of listed and complementary medicines comply with globally enviable manufacturing standards of PIC/S GMP for standardised plant-derived preparations; and have demonstrated the ability to rapidly pivot production under the COVID crisis in response to the Department of Industry's request for supplies. There is strong Government support to focus on opportunities that can be embraced by the Australian manufacturing sector and give Australian as a nation confidence to secure greater sovereignty in industry and healthcare.

Complementary Medicines Australia

CMA welcomes the opportunity to provide input into the proposed down-scheduling of medicinal cannabis preparations that contain cannabidiol as 98% of their cannabinoid content.

Complementary Medicines Australia is the peak body representing a thriving medicines sector supporting Australian jobs, research, manufacturing and exports by meeting community demand for preventative and complementary healthcare. The sector in Australia is a highly capable manufacturing industry required to comply with PIC/S GMP requirements including regular inspections, and strict mandatory pharmacopoeial and other TGA quality standards.

Australia's reputation for quality has over several decades evolved an industry that is:

- A greater than $5 billion industry
- Exporting more than $1 billion annually
- Employing more than 29,000 Australians, primarily in skilled technical professions
- Since 2018 the greatest exporter to China, above formidable rivals USA & Germany.

This makes Australia the source of the **highest quality manufacturing standards** in the world for finished product vitamins, minerals, and plant-derived preparations including standardised herbal extracts. Our manufacturers were able to respond rapidly to Government calls to increase production of hygiene supplies for COVID-19 risk mitigation, demonstrating the flexibility of supply to meet community need.

The Need for Quality Controlled, Accessible, Affordable Cannabidiol

The Senate Inquiry submissions and outcomes made it clear that the regulatory issue preventing access has become a humanitarian issue. The themes from the Senate Inquiry that accessibility and affordability are the key issues to be addressed via regulation.

The Senate Inquiry terms of reference included areas that are primarily relevant to this submission:

> (i) the **current status of the domestic regulated medicinal cannabis industry**;
>
> (j) the **impacts on the mental and physical wellbeing** of those patients struggling to access medicinal cannabis through Australia's regulatory regime;
>
> (k) particular **barriers for those in rural and remote areas** in accessing medicinal cannabis legally;
>
> (l) the **significant financial barriers** to accessing medicinal cannabis treatment;
>
> (m) the **number of Australian patients continuing to rely on unregulated supply** of medicinal cannabis due to access barriers and the impacts associated with that.

Senate Committee Recommendations

We note the Report and in particular, the relevant Recommendations 12, 13, and 20[1] of the Australian Senate Standing Committee on Community Affairs on the Inquiry to the current barriers to patient access to medicinal cannabis in Australia.

[1] List of Recommendations by the Australian Senate Standing Committee on Community Affairs on the Inquiry to the current barriers to patient access to medicinal cannabis in Australia

Recommendation 12

4.55 The committee recommends that the Therapeutic Goods Administration, as a matter of priority, conduct broad public consultation on the future scheduling of cannabidiol and other non-psychoactive cannabinoids.

4.56This public consultation should be conducted with the aim of the Department of Health making an application to the Advisory Committee on Medicines Scheduling, if deemed appropriate, and should therefore consider:

- the current inclusion of cannabidiol in the Uniform Scheduling of Medicines and Poisons (Poisons Standard) Schedule 4 – Prescription Only Medicine and other cannabinoids in Schedule 8 – Controlled Substance;
- the suitability of down-scheduling these cannabinoids to Schedule 2 – Pharmacy Medicine and/or Schedule 3 – Pharmacist Only Medicine; and
- the suitability of regulating these cannabinoids as complementary medicines, through removal from the Poisons Standard and inclusion in the Therapeutic Goods (Permissible Ingredients) Determination.

4.57 The committee is of the view that a safety review and public consultation process will provide the Therapeutic Goods Administration with the evidence required to determine the most appropriate pathway for the future regulation of cannabidiol and other non-psychoactive cannabinoids consistent with the requirements of safety and quality for all therapeutic goods in Australia.

Recommendation 13

4.58 The committee further recommends that, as soon as practicable after a safety review and public consultation process is completed, the Department of Health make any appropriate application to the Advisory Committee on Medicines Scheduling in relation to the down-scheduling or de-scheduling of cannabidiol and other non-psychoactive cannabinoids.

Recommendation 20

5.107 The committee recommends that the Australian Government, through COAG, encourage a review of state and territory criminal legislation in relation to:

- amnesties for the possession and/or cultivation of cannabis for genuine self-medication purposes

Safety Considerations supporting Unscheduling of Low Dose Cannabidiol

A main concern of the TGA safety review is possible drug interaction. This is an important observation that must be considered, but can be regulated in ways that do not overwhelm key objectives – compassionate and rapid supply of high quality of relatively affordable cannabidiol.

The extent of concerns around interaction does not appear to be sufficient to warrant scheduling. The WHO Expert Committee on Drug Dependence noted that while 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. Some drug interaction potential has been observed at 5-50 mg/kg/day[2] but there does not appear to be reports of interactions with very low dose CBD at 1 mg/kg/day.

There are other unscheduled ingredients such as *Hypericum perforatum* (St John's Wort) which have widely documented drug interactions and that have on a long-term basis been successfully managed through warning statements that are not in a CMI. If concerns remain, warning statements on unscheduled preparations can have prominence requirements applied, as is the case for substances such as royal jelly (3mm bold type font).The degree of concern does not appear to be of serious clinical significance to the extent it requires Pharmacist/Pharmacy intervention at this very low dose, and this is consistent with the requirements for safety and quality for all therapeutic goods in Australia.

[2] Qian et al [2019]: https://pubmed.ncbi.nlm.nih.gov/31433338/

Compassionate Health Considerations supporting Unscheduling Low Dose Cannabidiol

Removing low dose cannabidiol from the Poisons Standard would permit supply in Australia under controlled, high quality, TGA GMP conditions , and *also*;

- ✓ **Remove financial barriers** as much as possible for low dose non-PBS medicines;
- ✓ **Remove access barriers** for consumers including remote and regional areas;
- ✓ **Be realistic, rapid, and achievable**;
- ✓ **Reduce public health risks of ongoing illicit supply** by Australians seeking affordable supply through the non-PIC/S GMP manufacturers overseas;
- ✓ **Reduce public health risks of Australians growing their own cannabis** of unknown component profiles for personal medicinal use, as per Senate Recommendation 20: - that the COAG, reviews legislation to create amnesties for the possession/cultivation of cannabis for self-medication.
- ✓ **Would be expected to improve public health broadly –** if the submissions to the Senate Inquiry are relied upon, which presented compelling personal stories of the benefits of cannabidiol as a well-tolerated and relatively low risk product, significantly assisting people to physically and mentally function in their daily lives.

Pharmacist Only access of very low dose cannabidiol will not be able to achieve the humanitarian goals of access and affordability sought by the Australian Senate Inquiry, due to the lack of data at the specified dose to pass the hurdle of product registration. It could take over a decade for sufficient products to enter the market at a material volume that would see affordable access begin to occur.

Market limitations of registrations relative to the size of the demand, and resulting costs, in comparison to the already extensive “illicit” community use of unregulated cannabidiol or homegrown cannabis, appear to not improve public health outcomes when viewed from the broader perspective.

Australian manufacturers of listed and complementary medicines comply with strict manufacturing standards of PIC/S GMP relative to the global supply of plant-derived products. Removing cannabidiol from the Poisons Standard as proposed by the private application 2.2, can be appropriately mitigated by dose controls proposed as part of the TGA’s application 2.5.

The safety of unscheduled low dose access would be furthered by any additional controls required for medicine manufacturing, labelling and claims in the post-scheduling regulatory environment. This would most effectively occur by inclusion of the preparation at the request of the Minister onto the Permissible Ingredients Determination. Accompaniment by a TGA Monograph for claims, essential warning statements, and a requirement that it cannot be supplied in a medicine with other active ingredients for 3-5 years, can ensure health effects and pharmacovigilance can be monitored efficiently.

The use of a TGA Monograph, as recommended by the Review of Medicines and Medical Devices (MMDR), may provide wording if there are concerns about the level of evidence available. N=1 trials that may be set-up with Australian researchers may also provide significant insight whilst enabling more extensive research funds to go towards higher dose preparations and other types of medicinal cannabis.

In this way, a ‘hybrid’ proposal of the two existing applications applies multi-faceted controls on medicine risk reduction whilst reaching the humanitarian and compassionate objective sought by the Australian Senate.

Community Support for Unscheduled Cannabidiol: YouGov Galaxy Poll Key Findings

Methodology

A study was conducted on the YouGov Galaxy Omnibus between 15-18 May 2020. Sample comprised 1,034 Australians aged 18 years and older throughout Australia applying age, gender and region quotas.

Attitudes to the Australian Government making it easier for consumers to gain access to safe, high quality, medicinal cannabis (cannabidiol(CBD), without a prescription:

- **Two thirds (66%)** of Australians would support the Australian Government's decision to make it easier for consumers to gain access to safe, high quality, medicinal cannabis (cannabidiol(CBD), without a prescription, **including 41% would strongly support such a decision**.
- Only 13%, the equivalent of 2.5 million people, opposed the decision for greater access, including **only 5% that strongly opposed it**.
- Australians age 50-64 years are more likely than all other age group to strongly support the decision for great access (50-64 50% compared to 65+ 37%, 35-49 44% and 18-34 34%).
- For those that have used complementary medicines to treat or manage a chronic condition support is stronger, as they are more likely than those who have not to say they support the Australian Government's decision to make it easier for consumers to gain access to safe, high quality, medicinal cannabis (cannabidiol(CBD), without a prescription (73% compared to 61%).

Regarding the likelihood of purchasing products containing CBD if they were more freely available:

- Four in ten (41%) Australians, the equivalent of 8 million people, say they would be likely to purchase products containing CBD if they were more freely available, including one in five (20%) that say they would be very likely.
- Likelihood to purchase is significantly higher among those aged 35-49 years, with one in four (26%) of them saying they would be very likely to purchase products containing medicinal cannabis (CBD) if they were more freely available.
- For those that have used complementary medicines to treat or manage a chronic condition likelihood to purchase is stronger, as they are more likely than those who have not to say they would be likely to purchase products containing CBD if they were more freely available (52% compared to 37%).

Consumers inform doctors of complementary medicine use which could be furthered by warnings.

- Of those that have used a complementary medicine to treat or manage a chronic disease/condition, the majority (78%) have informed their doctor/GP that they are taking them, including 63% who are aware of all complementary medicines that they are taking and 16% that are only aware of some of the complementary medicines that they are taking.
- More than one in five (22%) have not made their doctor/GP aware, however this is largely due to having never thought of mentioning it or having never been asked (19%).

Scheduling Proposal for rapid, safe access (hybrid of TGA & Private proposals)

Scheduling Proposal	Comment
• Unscheduled	Freely available for consumer and health professional access, with high safety, quality, and efficacy control (post-scheduling controls).
• CBD >98% of cannabinoids • Any other cannabinoids <2% and naturally occurring	• As per World Health Organization (WHO) preparation • As per TGA Safety Review / Scheduling Proposal
• Adults only	• As per TGA Safety Review / Scheduling Proposal
• 30 day pack	• As per TGA Safety Review / Scheduling Proposal
• 1mg/kg/day	• As per TGA Safety Review / Scheduling Proposal
• 90mg/day maximum: Undivided preparations OR tablets/capsules 30mg or less	An average Australian male is 87kg (ABS) Permits dose adjustment for body weight, therapeutic effect or mild side effects.

Post-Scheduling controls to support removal from Poisons Standard

Listed Medicine Approval	Comment
Affordable, competitive access: ★ **Minister-led approval of CBD as a "Permitted Ingredient" [3].**	Minister-led approval of CBD preparations examined by TGA and WHO, for 'Listed Medicines', allows rapid competition by Australian manufacturers without exclusivity. The public would be able to access high quality, low cost CBD products in the very near future.
Safety ✓ Clear warnings ✓ CBD single-active ✓ Plant-derived	Low dose CBD is thought to be reasonably well-tolerated. Single-active CBD helps monitor safety. Effective warnings decided by public consultation. Drug interactions may be controlled as for other products, *e.g. 'St John's Wort affects the way many prescription medicines work - including oral contraceptives. Consult your doctor.'*
Quality ✓ GMP Manufacturing ✓ Required Conditions ✓ TGA Standard for Medicinal Cannabis (TGO 93)	Australia has an international reputation for high quality complementary medicines such as vitamins and herbs. Australian GMP-licensed manufacturers are highly capable and ready to supply high-quality lower-cost CBD for Australian consumers.
Use/Presentation: ✓ TGA Monograph -approved claims ✓ 'N=1 trials' via app for clinical data	Government decides on specific wording of allowed claims for CBD to help ensure it can become widely and easily available at a low cost in the very near future. "N=1 trials" via a voluntary app can gather efficacy and safety data for Australian researchers.

[3] Section 26BC of the *Therapeutic Goods Act 1989* provides the Minister authority to do so of his or her own initiative.

Proposed Scheduling entry

Below is a Scheduling entry that proposes modifying the TGA entry 2.5 to remove a specified preparation from the Poisons Standard in line with proposal 2.2, to create a hybrid proposal for oral use. The suggested amendments to proposal 2.5 are either struck through or highlighted:

Cannabidiol

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
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;

except when ~~included in Schedule 3.~~

~~**Schedule 3 - New Entry**~~

~~CANNABIDIOL in preparations for therapeutic use when:~~

a. the cannabidiol is either plant derived, or when synthetic only contains the (-) CBD enantiomer; and

b. the maximum recommended daily dose is 90 mg or less of cannabidiol; and

c. the preparation is only an undivided preparation or in divided preparations each of 30mg or less;

[d]. in packs containing not more than 30 days' supply; and

[e]. cannabidiol comprises 98 per cent or more of the total cannabinoid content of the preparation; and

[f]. 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

[g]. for adults aged 18 years and over.

We also support the removal of low-concentration cannabidiol for topical use. We are aware that other submitters are providing this information and that the summary of evidence is such that topical use in unscheduled preparations does not present a risk of harm, but may be useful in low risk skin conditions such as mild acne; consequently we support the addition of:

; or [h]. for topical only use at a labelled concentration of 5% or less cannabidiol.

Comparison of CMA hybrid proposal to the current amendment applications

	A. Australian Government/TGA	B. Private Applicant	C. CMA Submission
Access	**Pharmacist Only (Schedule 3).**	✓ **Unscheduled**, ready consumer access.	✓ B; Additional scheduling/post-scheduling controls on dose, safety, quality, claims.
Regulatory level	'Registered' (AUST R) medicine – TGA pre-approved – must obtain clinical trials proving effectiveness at the 60mg dose before it can be approved.	✓ Eligible to become either 'Listed', 'Listed Assessed' or 'Registered'.	✓ B.
Cannabinoids	✓ **98% cannabidiol** or more of total cannabinoid content		✓
Other content	✓ 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.	Contains less than or equal to 0.2 per cent tetrahydrocannabinol (THC).	✓ A.
CBD source	✓ Plant derived; or ✓ Synthetic, if it only contains the (-) CBD enantiomer	Whole plant cannabis product or distillate or isolate. (Synthetic or semi-synthetic CBD as prescription only.)	✓ A. Noting only plant derived complementary medicines should be eligible to become Listed/Listed Assessed Medicines.
Maximum daily dose	**60mg** (1mg/kg/day)	Not specified.	✓ (1mg/kg/day) **90mg** from: ✓ **Undivided preparations,** *or* ✓ **Divided preparations each 30mg or less** Based on ~1mg/kg/day and ABS 2018 data that the typical Australian male weighs **87kg** and the typical female **72kg.** Divided dosing – Adjust for weight, therapeutic effects or mild side effects.
Pack size	✓ **30 days** supply.	Not specified.	✓ A.
Age	✓ **Adults** 18 years or **older**	Not specified.	✓ A.