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To the Committee Secretary, Senate Legal and Constitutional Affairs Committee ***Friday 13 March 2015***

Please find a brief submission to the Committee's Inquiry below.
We give evidence in the following capacities:

Dr David Allsop

- Senior Research Fellow in Psychopharmacology and Addiction Medicine at the University of Sydney.
- Conjoint Lecturer at the National Drug and Alcohol Research Centre (NDARC), University of New South Wales.
- Honorary Senior Research Fellow, Langton Centre, Sydney Hospital.
- Honorary Senior Research Fellow, Drug Health Services, Concord Hospital.
- Clinical Trials Coordinator trained in Good Clinical Practice with specific experience in cannabinoid clinical research including regulatory controls for working with cannabinoids in humans, clinical protocol development and sourcing and dosing of cannabinoid medicines.

Clinical Associate Professor Nick Lintzeris

- Addiction Medicine Specialist (FAChAM) and researcher (PhD, Epidemiology & Population Health, ANU). Clinical Associate Professor, Division Addiction Medicine at Sydney University since 2008.
- Director Drug & Alcohol Services, SESLHD (based at The Langton Centre) since 2010.
- Chief Addiction Medicine Specialist, Mental Health Drug Alcohol Office, NSW Health 2011-2013.

Associate Professor Jonathon Arnold

- Associate Professor in Pharmacology, University of Sydney.
- Director of the Cannabinoid Research Group, Brain and Mind Research Institute, University of Sydney.

Professor Iain McGregor

- Professor of Psychopharmacology, University of Sydney.
- NHMRC Principal Research Fellow, University of Sydney.
- Director of the Psychopharmacology laboratory, School of Psychology, University of Sydney.

We are available to provide personal evidence if that would assist the Committee.

Yours sincerely
Dr David Allsop
A/Professor Nicholas Lintzeris
A/Professor Jonathon Arnold
Professor Iain McGregor

EXECUTIVE SUMMARY

- The current regulatory framework for cannabis and cannabis based medicines in Australia makes research and development activities slow and expensive

- Much of the research cited for the lack of efficacy of medical cannabinoids is based on outdated experiments that used suboptimal cannabinoid preparations (i.e. synthetic orally administered THC only) with limited preclinical or early clinical workup to aid in dose optimization

- The new science of medicinal cannabis is only beginning to emerge, with a wide range of non-psychoactive, non-addictive cannabinoid molecules exhibiting exciting medical promise

- Our group has nicknamed the top ten most interesting non-psychoactive, non-addictive cannabinoids "the big 10" – including CBD, CBDA, CBDV, THCA, THCV, THCVA, CBG, CBGA, CBN, CBC. We believe that the big 10 should not be scheduled along with THC in Schedules 8 or 9 owing to their lack of psychoactive effects or addictive potential. The proposed new regulator of medicinal cannabis could be more nimble than the TGA in responding to emerging new evidence, helping to fast track research and development activities in cannabinoid medicine

- Medicinal cannabis use is widespread in Australia despite the prevailing regulatory framework. Vulnerable patients source cannabis preparations from the black market. These preparations are unregulated with potential for inappropriate cannabinoids for certain indications (e.g. high THC for pediatric epilepsy), contamination with pesticides or heavy metals, tinctures with no cannabinoids sold as medicine, and poor understanding of appropriate dosing schedules. These safety concerns could be controlled by the Regulator to help deliver safe and reliable cannabis based medicines to those who would benefit

- We believe that old attitudes and a restrictive policy environment need to change to keep pace with the new science of medicinal cannabinoids

- We fully support this bill and its proposition to establish an independent regulator of medicinal cannabis

Submission to Inquiry into the Regulator of Medicinal Cannabis Bill 2014

Introduction

Cannabinoid science is one of the fastest moving frontiers in pharmacology and is poised for a period of great scientific and medical discovery in coming years. This is based on our relatively new understanding of the *endocannabinoid* system of the brain and body. Endocannabinoids are cannabis-like signalling molecules that play a role in nearly every physiological process that is known to mankind. Endocannabinoids act through cannabinoid CB1 and CB2 receptors to influence appetite, cognitive function, pain, anxiety, immune function, bone growth and tumour proliferation. The development of medicines that modulate these processes has remarkable potential to influence human disease and wellbeing.

Collectively, our team has more than 70 years of research experience, and more than 50 peer-reviewed scientific publications, in the area cannabinoid research. This involves studies conducted with cells, laboratory animals and human participants. We are part of a broader network of scientists and clinicians in Australia and overseas who are actively researching the potential therapeutic applications of cannabinoids. Over the past decade there has been immense international growth in this area of research as the significance of the endocannabinoid system in human health and disease becomes increasingly apparent. Despite this, we conduct our research in a tight regulatory environment that makes sourcing, holding and administering cannabinoids extremely difficult and expensive. Cannabinoid preparations typically have to be imported from the USA or Europe at great expense, and with time consuming paperwork and processes imposed by the TGA and state regulatory authorities. This is despite the fact that the vast majority of cannabinoids we research have no psychoactive or addictive properties in humans.

Medical cannabis (or the more neutral term *medicinal cannabinoids*) encompasses the therapeutic use of cannabinoid molecules derived from the cannabis plant, including:

1) pure phytocannabinoids (e.g. THC, CBD, THCA, CBDA, CBDV)

2) synthetic analogues of phytocannabinoids (e.g. the medicine *Nabilone,* synthetic CBD).

3) pure phytocannabinoid drug combinations (e.g. oils and tinctures extracted from cannabis plants)

and,

4) cannabinoid extract formulations like *Sativex* that contain consistent doses of THC and CBD that have been manufactured according to strict and consistent pharmaceutical standards.

Understanding the cannabis plant and the phytocannabinoids

Unfortunately, much of the contemporary debate surrounding medicinal cannabis and the role of cannabinoids in medicine remains fixated on the potential harms of the main psychoactive ingredient of cannabis, THC. This is an outmoded view that is in urgent need of revision.

The cannabis plant's therapeutic potential goes far beyond the effects of THC and recent evidence shows without a doubt that major therapeutic effects can be obtained via the many different non-psychoactive cannabinoids, and related terpenoids, that are present in the plant.

Cannabis sativa contains more than 100 different cannabinoid constituents (e.g. CBC, CBG, THCV, CBDA). Many of these are not psychoactive, like cannabidiol (CBD), and emerging evidence suggest that many of these compounds given alone, or in combination, may be effective in treating diseases that are often very difficult to treat, such as childhood epilepsy, neuropathic pain and cancer. Table 1 provides a brief and non-exhaustive summary of some of the potential applications.

Cannabinoid	Intoxicates?	Possible Medicinal Application
THC	√	Nausea and Vomiting, Muscular Spasms, PTSD, Pain, Cancer, Inflammation,
CBD	*x*	Epilepsy, Psychosis, Anxiety, PTSD, Addiction, Dementia, Cancer, Insomnia
CBDA	*x*	Epilepsy, Nausea and Vomiting, Cancer
CBDV	*x*	Epilepsy
THCA	*x*	Nausea and Vomiting, Epilepsy
THCV	*x*	Diabetes, Obesity, Pain, Inflammation, Epilepsy
THCVA	*x*	Uncertain at present
CBG	*x*	Glaucoma, Cancer, Inflammation, Anxiety, Huntingdon's Disease
CBGA	*x*	Uncertain at present
CBN	*x*	Anxiety, Insomnia, Epilepsy, Anti-bacterial effects
CBC	*x*	Pain, Inflammation, Cancer

Table 1. *THC and the big 10 non-psychoactive cannabinoids, showing probable efficacy across different diseases.*

Within our research group we refer to the 10 most promising non-psychoactive cannabinoids (listed in Table 1) as the "big 10". A primary mission for our group over the next few years is to establish a Centre for Medicinal Cannabinoid Research at the University of Sydney to further explore the therapeutic potential of the "big 10" in treating a range of diseases such as pediatric epilepsy, cancer, neuropathic pain, dementia, addictions and mental illnesses such as depression and schizophrenia. This endeavour is

receiving strong support from within our University and interest from philanthropists. The work of the centre will involve a rich network of basic scientists and clinicians. We are hopeful that the federal and state regulatory environment might change to expedite the sourcing of non-psychoactive cannabinoids, extracted from locally grown hemp, to facilitate this major new research endeavour.

Cultivation and production of cannabis and its products for medical uses

We therefore believe that this bill's proposed mandate of setting up system for the cultivation and production of cannabis for medical use and research in Australia, based on the Tasmanian poppy industry for opioids, would greatly accelerate basic, clinical and translational research in the cannabinoid area. This not only has the potential to facilitate access to medicinal cannabinoids for the research and broader community, but also may help position Australia as a global leader in the fast moving area of cannabinoid therapeutics.

At present, legal access to plant-derived cannabinoids is extremely limited in Australia. Easing restrictions on growing cannabis for research purposes would provide Australia a local and ready supply of cannabinoids for medical research purposes. The development of innovative cannabinoid medicines would not only help patients, it would also put Australia at the forefront in the commercialization of cannabinoid medications. Cannabinoid therapeutics has already evolved into a billion dollar industry.

Furthermore, the bill enhances safety for members in the community – by removing legal sanctions for those using medical cannabis products, and importantly, by enabling some degree of certainty for consumers of the content of such products.

In 2013, in conjunction with the NSW Police and the National Drug and Alcohol Research Centre (NDARC), our group preformed the first ever chemical analysis of street cannabis seized by the police at various sites in NSW (Swift et al, 2013). Our results showed that typical street cannabis (more than 200 samples were analysed) was high in THC and very low in the therapeutically useful, non psychoactive cannabinoids such as CBD and THCV. This illustrates a major potential problem with the current regulatory environment whereby person seeking to use medicinal cannabis are likely to end up with illicitly obtained, high THC preparations, that may be devoid of the phytocannabinoid ingredients that would best treat their condition.

The situation in the USA is becoming much more nuanced, such that a wide variety of cannabis strains are available with differing levels of cannabinoids, some (e.g. Charlotte's Web) optimised to contain virtually no THC whatsoever, but high levels of non-psychoactive therapeutic cannabinoids such as CBD and CBDA. As we develop a greater understanding of the role of different "big 10" cannabinoids (e.g. CBD, THCV) for different medical indications (e.g. epilepsy, chronic pain, neurodegenerative conditions, PTSD, obesity, cancer), we will need to grow strains of cannabis that maximize the content of these cannabinoids to facilitate therapeutic efficacy and the extraction and purification of these compounds for high quality

medications. At present, consumers have no ability to determine the type or strength of cannabinoid products they are consuming, and it remains illegal for analytical laboratories to even test these products. These are major impediments to the safer use of medical cannabis, and may more than likely exacerbating the harms experienced by consumers.

Establishing a medical cannabis regulator independent of the TGA

We agree with the establishment of a medical cannabis regulator that is independent of the TGA, and that has specialist scientific and clinical knowledge of the cannabinoid field. There are many cannabinoid researchers and clinicians within Australia who are international leaders in this field and in a position to assist with this important mission.

The regulator can establish rules for licensing the production, manufacture, supply, use, experimental use and import and export of medicinal cannabis. Knowledge of the optimal phytocannabionids for treating different disease states will allow different strains to be grown that maximize content of specific phytocannabinoids or their combinations. We are aware of local sources within the industrial hemp industry that hold germplasm for more than 200 different strains of cannabis, with widely varying levels of big 10 cannabinoids. A related endeavor is to manufacture new medicines based on these non-intoxicating cannabinoids and we have heard interest from natural product companies such as Blackmore's to diversify into this potentially important and lucrative area.

We understand that Western Australia and Victoria have recently approached the TGA with proposals to reschedule cannabidiol (CBD), one of the most important non-intoxicating cannabinoids, from schedule 8 to schedule 4 – in recognition of its strong medical potential across a variety of disease states and lack of addictive or harmful properties.

As noted above, many other non-psychoactive cannabinoids are of major interest and their lack of addictive potential and intoxicating properties means that many of the current regulatory barriers to their procurement and storage are completely unnecessary. Such regulation reflects historic concerns regarding cannabis, an era that is prehistoric relative to our current understanding of the pharmacology of the cannabinoids and the endocannabinoid system.

We believe that a dedicated medical cannabis regulator can coexist in parallel with the TGA's existing procedures and processes but provide a much more lean, efficient and specialized approach to regulation. While there is a role for medical cannabis products as identified in this bill, it does not obviate the role of the TGA in the development of medical cannabinoids as pharmaceutical products. Pure pharmaceutical grade products will be an inevitable result of the current research trajectory in the medicinal cannabinoid area and may be the most desirable end product for certain patient populations. The new regulator can explore alternate yet parallel and synergistic policy models for the regulation of

research into medical cannabis products, as well as their use.

Inclusion of cannabis flowers and derived medicinal products from the plant

We feel that the bills inclusion of cannabis products that include the flowers of the plant or any synthetic product derived from the plant is important to enable the most comprehensive screening and development of targeted cannabinoid therapeutics. We would like to clarify that novel medicines may also take the form of purified (non synthetic) botanical products, as is seen with Sativex, or nonphytocannabinoid based synthetics that modulate the endocannabinoid system with distinctive, non-cannabinoid chemical structures.

Potential impact of this new legislation on cannabinoid science in Australia

As scientists and clinicians involved in the development and testing of new medicines, we believe that this legislation is a significant and welcome development in regulating cannabis and its derivatives for therapeutic purposes in Australia at this time. Whilst considerable more research is required to better understand the safety, effectiveness and ultimately the role of different cannabinoid products for different clinical indications, the current illegal nature of all cannabis products in Australia, including the non psychoactive, non addictive molecules, are a major impediment to further research and development. This bill will enable the development of a local regulated cannabinoid industry that can develop and supply different cannabinoid products (e.g. CBD, THCA, THCV, THCVA, CBG, CBGA, CBDA, CBDV, CBN, CBC), rather than relying upon access from international pharmaceutical companies – which will always prove difficult, time-consuming and expensive. The supply of suitable botanical cannabinoids developed under good manufacturing processes here in Australia will greatly assist further research in this area, as well as enhance the local economy.

As researchers currently engaged in studies using medicinal cannabinoids (e.g. Sativex) we are aware of the many complex barriers to conducting research and delivering treatment under current regulations. This legislation will greatly advance the potential for much needed research in a diverse range of clinical fields, including cancer, chronic pain, neurodegenerative conditions (such as Alzeimers and Parkinson's), obesity, chronic inflammatory conditions (e.g. irritable bowel, rheumatoid arthritis) and mental health disorders (such as addictions, PTSD and early psychosis). Advances in the science of cannabinoids in the past decade means we are at the threshold of significant clinical developments with the cannabinoids.

Caution and harms of cannabinoids

We do recognise that, like all medicines, cannabinoids are also associated the potential for a range of adverse events, and there need to be suitable protections and reliable consumer information for the community, as well a pathway for further research that refines our knowledge and improves safety and effectiveness with these products. A regulated industry is far preferable to the existing situation of consumers relying on unregulated and illegal products, no authoritative consumer information from health professionals, and researchers being restricted to pharmaceutical products – of which there remain a very limited number of cannabinoids available from a small number of pharmaceutical companies.

The illicit use of cannabis products for therapeutic indications appears common in many sections of the Australian community, despite existing legal sanctions. Evidence regarding the safety and efficacy of cannabinoids for therapeutic indications is still emerging - this is a burgeoning area of interest in both preclinical and clinical research, which to date has been hampered by limited access to appropriate cannabinoid products. On balance the potential benefits of such an endeavour as this bill outweigh the risks in our opinions. This legislation ensures that medicinal use of cannabis will still be tightly regulated under the new administration, with a number of important safeguards that are currently absent in the unregulated illicit cannabinoid market. We also believe that the role of the Therapeutic Goods Administration pipeline should remain intact regarding the development of pharmaceutical grade medicines derived from the cannabis plant.

Regulatory lessons from other jurisdictions

Medical cannabis has been introduced in the US, Canada, Netherlands, UK, Israel, Czech Republic, Uruguay, Spain, Australia (the New South Wales terminal illness scheme) with different models of regulation. These are significant developments allowing patients access to the therapeutic benefits of cannabis. However numerous problems have arisen with many due to policy inconsistencies. For example, in some models, patients possessing medical cannabis may be free from criminal prosecution, however the cultivation and supply of cannabis still remains illegal. This raises an obvious problem - how do patients then gain access to medical cannabis, and what quality controls exist to minimise harms to the consumer and broader community? Some of the problems arising in different jurisdictions include:

1) The demand for medical cannabis outstrips supply. In the US and Spain this has been overcome somewhat by allowing patients to use street cannabis via buyer's clubs, which itself is associated with a different set of issues. Unregulated supply of street cannabis is suboptimal because street

cannabis is likely to have high THC content, which is suboptimal for many medical indications. It may also have toxic contaminants (e.g. pesticides, heavy metals) and the predominant mode of administration of street cannabis is smoking. Moreover, variability in the amount of cannabinoids found in the plant may undermine optimal dosing and therapeutic efficacy without tight regulation.

2) Many doctors will not prescribe or recommend medical cannabis as they are confused about its specific indications and are concerned about litigation that might arise from recommendations to use an illegal drug. Regulatory reforms and better health professional education is required.
3) The medical cannabis supply system has been exploited by recreational users to maintain their habit rather than treat medical condition.

Some have argued that most of these problems would be diminished if cannabis were made legal for both recreational and medical applications – there would be no issue of supply and the user would then take personal responsibility for any adverse effects the drug. However we believe this to be an overly simplistic argument - legalisation for recreational purposes (and medical indications) and the promotion of 'street' cannabis does not necessarily progress the refinement and development of cannabinoids for medical indications – it merely makes street cannabis available. The proposed legislation under consideration here better addresses the objective enhancing availability of cannabis products for therapeutic indications.

Medical cannabis in its current form in the US is concerned with the medical applications of unregulated plant material that will most often be smoked. However, whole plant medical cannabis can in fact be regulated to a very high standard, with Good Manufacturing Processes and analytical checks to ensure consistent levels of known cannabinoids targeted in the plant breeding step of the pipeline. Such a regulated whole plant approach to medical cannabis is seen in the Netherlands, specifically with the company Bedrocan, as well as Canada operating a similar model.

Conclusions

There are still many issues that remain unresolved regarding the use of cannabinoids for medical purposes – which cannabinoids, used for which conditions, how are supplies accessed and what protections are in place for the consumer, how do we develop the evidence to inform consumers and health practitioners. It is not possible for all these to be definitively addressed at this point in time. What is needed is a framework that enables this work to develop, and to move beyond the current prohibition of all cannabis products other than one pharmaceutical product licensed in Australia. We believe that this proposed legislation is a step in the right direction, providing a range of safeguards.

Research and development of medical cannabinoids has also been stymied by its illegal status and

prohibited drug scheduling. This has placed roadblocks in the way of obtaining the required compounds and conducting research on these agents. Moreover, funding for cannabinoid research and clinical trials on cannabinoids has been limited and is sorely needed. Much of the current evidence concerning the therapeutic efficacy of the cannabinoids has focused on THC, which is psychoactive, and to a lesser extent cannabidiol (CBD), which is non-intoxicating and holds much therapeutic potential. However there are more than 100 non-intoxicating cannabinoids from the plant with promising therapeutic potential, yet to be examined for their medical properties, for example CBDA, CBDV, THCV, THCA, THCVA, CBG and CBC. Current legislation groups all of these cannabinoids under Schedules 8 or 9 in Australia, even though these drugs do not have psychoactive properties, have no addictive potential, and yet have promising therapeutic benefits on preclinical and early stage human explorations. The future of medical cannabinoids looks bright - but it could be brighter with a relaxation of legal restrictions on research and development and therapeutic usage, and we generally support this proposed legislation.