19th April 2015

Victorian Law Reform Commission
GPO Box 4637
Melbourne, Victoria
Australia

Email: law.reform@lawreform.vic.gov.au

RE: Public Submission in response to the Victorian Law Reform Commission Medicinal Cannabis: Issues Paper

In response to the questions posted in the "**Victorian Law Reform Commission Medicinal Cannabis: Issues Paper**". Our group welcomes the opportunity given to help the commission in the assessment of a Law Proposal on Medicinal Cannabis by answering the questions presented at the end of the issue paper with the aim of contributing by giving helpful advices thanks to our expertise and knowledge within the queries raised.

The group is represented in this letter by Sergio Pagliazzi, Chief Executive Officer of Under The Tree Biopharmaceuticals Pty Ltd. and Secretary of the newly established European Network of Therapeutical Cannabis Research supported by Veronesi's Foundation. We are working in collaboration with Yehuda Baruch, Head of Research and Regulation of One World Cannabis Ltd. whom shall propose their view in a separate statement.

Besides, the group is supported in this submission by influential members of organisations such as University of Melbourne, Neuroscience Trials Australia, IEO (European Institute of Oncology) and Veronesi's Foundation. Between these our colleagues and scientific advisors such as Professor Terence John O'Brien, The James Stewart Chair of Medicine and Head of the Department of Medicine at The Royal Melbourne and Western Hospital and at The University of Melbourne, Dr Tina Soulis, General Manager of Neurotrials Australia and Prof. Umberto Veronesi, founder of the above mentioned Foundation and of the IEO, renowned oncologist and former Italian Minister of Health.

The Medicinal Cannabis program in Israel is thought to the best model to follow, and has been the inspiration for other models which are been designed in Europe and North America. Dr. Yehuda Baruch was the head of the Medicinal cannabis program in Israel for ten years and designed to implementation

the entire program. He is consulting with Canadian authorities regarding the Medicinal Cannabis Program in Canada, was a key player for education programs on medical cannabis for the medical staff established in Czech Republic and helped designing their model for the Medicinal Cannabis Scheme.

UTT Biopharmaceuticals Pty Ltd has collaborations with top scientists in the field of Cannabis Science, and has highly experienced and skilled personnel who are currently active in the Pharmaceutical Sector. They have the know-how of how to operate within the industry guidelines and following quality by design principles, which would be applicable to the production and distribution of Medicinal Cannabis same as for any Pharmaceutical Grade Product.

The group actively supports the Victorian Law Reform Commission's efforts to devise a legislative scheme to start up the Medicinal Cannabis Program within the state, which could serve as a model for the rest of the Commonwealth. There are many patients who are in dire need of the treatment options offered by Medicinal Cannabis, and many more who could attain much benefit for the scheme. The responses to the questions have been made in the context of the experience and knowledge of the members of this group in dealing with issues raised by the Medicinal Cannabis: Issues Paper.

Listed below in this document we added an annex with the Questions presented in pages 170-171 of the "Medicinal Cannabis" Issue paper issued by the Victorian Law Reform Commission with the subsequent responses, answered in a concise fashion.

We wish to thank again the Commission for giving us the right to present our opinion to the public. The group is more than willing to offer their services to Law Reform Commission, and can be contacted by writing at: sergio.pagliazzi@uttbio.com or abdul.mohammad@uttbio.com

Yours Sincerely,

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ANNEX - Questions

1) Which of the following considerations should determine whether or what are exceptional circumstances for medicinal cannabis to be made available to a patient:
(a) The circumstances of the patient
(b) The state of clinical knowledge about the efficacy or potential efficacy of using cannabis in treating the patient's condition
(c) Both of the above?

As with any Pharmaceutical Drug or Medicinal Preparation, there has to be enough of a Pharmacological Rationale for it be prescribed by Medical Practitioners. There should be enough clinical data with regards to the Safety, Efficacy and Dosage of the Medicine in order for it to be used- which are requirements set by regulatory bodies such as the TGA. Similarly the same model should be applied to the use of Medicinal Preparation of Cannabis.

The only way any clinical knowledge can be generated, is for the initiation of clinical trials in all areas of interest and conduction of concurrent preclinical studies. From small-scale to large-scale nationwide studies, participants can be analysed for Efficacy and at the same time there will also be a lot of pathological data to delve deeper into why the medicinal cannabis is working. It is necessary to involve actively Universities, creating a decentralized research network that will permit to design experiments concurrently in vitro/In vivo studies conducted in the top Biomedical Institutes in Australia, discoveries in the field of cannabinoid science would be imminent. These discoveries would enhance the scientific basis for a specific preparations of medicinal cannabis, which will be designed to target specific diseases.

For a patient to have access to medicinal cannabis requires a recommendation from a specialized medical practitioner, and it should be treated as nutraceutical or pharmaceutical drug. Medicinal cannabis should not be treated as an alternative therapy but should be evaluated clearly since it has shown in several studies and anecdotal cases to be more effective and safer than conventional pharmaceutical drugs for the some diseases. This is relevant in the case of intractable forms of epilepsy such as Dravet syndrome and Lennox-Gasteut syndromes, for which a treatment based on Cannabidiol-enriched cannabis preparations has shown to be highly efficacious (Porter and Jacobson 2013), and have a fewer side effect profile than conventional Anti-Epileptic Drugs (AEDs). Henceforth, a sufferer of one of these conditions should be prescribed or put on Medicinal Cannabis as the first option. The same justification applies to sufferers of Opioid-Resistant Pain, Nausea-induced by chemotherapy, Chronic Pain and Eating Disorders (Anorexia and Cachexia). Highly regulated Medicinal Preparations of Cannabis provide safer and more effective treatment options for sufferers of these diseases. The Medicinal Cannabis Preparation would be designed specifically for each of these diseases, with special

consideration taken into monitoring the levels of contaminants, especially THC due to its psychoactive properties. For some diseases like Epilepsy, THC would have to be absent from the preparations whereas it would have to be kept at determined / specific levels for the other conditions, since it may cause unwanted psychiatric symptoms at high concentration; defining the right dosage is very important to determine the threshold for psychoactive effects to arise in humans (Bhattacharyya, Morrison et al. 2010).

The availability of Medicinal Cannabis should be determined on the basis of the clinical knowledge of its safety and efficacy profile on the target disease. Where there is a lack of clinical knowledge, the Medical community should work together to engage in nationwide clinical trials to generate sufficient clinical data. Various associations exist and others are starting-up, with the aim of creating a large research network that shall help exchanging data and improve science base knowledge. Clinical trials are the best way to engage in swift action over this area of science, and are the best way to clear up any discrepancies over the use of Medicinal Cannabis.

2) For what conditions is there sufficient knowledge of the therapeutic benefits, dangers, risks and side effects of cannabis to justify allowing sufferers to use it lawfully in Victoria?

The most well-known and recently documented case of the therapeutic effect of Medicinal Cannabis is with Paediatric Epilepsy. The story of Charlotte Figi (Young S 2013) and other children treated with CBD-enriched Cannabis has really gathered the interest of scientists in the recent past. Pure CBD based drug (Epidiolex, GW Pharmaceuticals) or CBD enriched preparations showed promising effects in reducing seizure frequency, producing seizure freedom in some and provided beneficial therapeutic effects such as improved mood and sleep. There were minimal side effects such somnolence, drowsiness, fatigue and mild gastric pain (Cunha, Carlini et al. 1980, Porter and Jacobson 2013). GW pharmaceuticals is currently undergoing Phase 3 trials in the USA for Epidiolex as anti-epileptic / anti-seizure drug, which has been developed on the basis of the evident pre-clinical and clinical data.

For Chemotherapy Induced Nausea and Vomiting (CINV) there is evidence that cannabinoids have antiemetic properties, for which appetite inducing drugs based on THC have been developed (Rocha et al, 2008)(Rocha, Stéfano et al. 2008). Synthetic analogues of THC were found to be more effective than conventional anti-emetics in controlling nausea induced by chemotherapy (Tramèr, Carroll et al. 2001). However considering the use of THC, the side effects were mainly psychotropic such as dizziness, dysphoria, paranoia and Hallucinations (Tramèr, Carroll et al. 2001). Although THC has clear therapeutic value, its use is also riddled with complications-which are mainly psychotropic. The best

way to administer THC and negate its psychotropic effects is to co-administer CBD, which has shown to have antipsychotic effects in relation to the psychotomimetic effects of THC (Bhattacharyya, Morrison et al. 2010). Several studies shows the ability of CBD to antagonise THC psychotropic properties and balance the negative impact of THC administration thanks to CBD anti-psychotic effect; CBD inhibits THC metabolism by blocking its conversion to the more psychoactive form 11-hydroxy-THC by cytochrome P4503A11 (Bornheim 1995, Bornheim and Grillo 1998, Zuardi 2006, Hazekamp 2009). Sativex (which has a 1:1 THC:CBD ratio) showed to be effective in reducing CINV, and therefore producing similar formulations could be a way in reducing THC psychotropic effects. Sativex, developed by GW pharmaceuticals, was originally designed to treat muscle spasms and is currently tested for spasticity common symptoms of neurodegenerative disease such as Multiple Sclerosis (MS) or Amyotrophic lateral sclerosis (ALS), and has shown to reduce these symptoms in patients with MS (Collin, Ehler et al. 2010, Novotna, Mares et al. 2011, Notcutt, Langford et al. 2012). The most common side effects found during clinical trials were dizziness, somnolence and fatigue. There were very few psychiatric disorders, however elevated levels were seen in the Placebo group as well (Collin, Ehler et al. 2010). Opioid resistant cancer pain as well as neuropathic pain are two other conditions that could be potentially treated by Medicinal Cannabis Preparations. A cannabis extract with similar THC:CBD concentration levels showed to be efficacious for the relief of pain in patients with opioid resistant cancer pain (Johnson J R, Burnell-Nugent M et al. 2010), with moderate side effects. Low doses of vaporized Cannabis produced clinically significant analgesia in subjects with neuropathic pain, in which conventional treatments were used concurrently, and there were minimal or no side effects (Wilsey, Marcotte et al. 2013). Therefore Cannabis extracts could be administered as an alternative analgesic to conventional opioids, and are considered much safer. This is demonstrated by the fact that in the states of USA in which Medical Cannabis has been legalized, have shown significant reduction of opioid related overdose death rate compared to states in which Medical Cannabis is still illegal (Bachhuber, Saloner et al. 2014).

Medicinal Cannabis has also shown to have potential in treating anorexia-cachexia, caused by diseases such as cancer or AIDS. Cannabis extracts showed to increase appetite in patients suffering from anorexia-cachexia, and much more so than just pure THC (Strasser 2006). Dronabinol, a synthetic pharmaceutical formulation of THC, has shown to be a successful treatment option for anorexia (Andries, Frystyk et al. 2014). There is evidence from pre-clinical studies, small experimental studies and anecdotal cases that the Medicinal Cannabis can have therapeutic effects for disorders such as Cancer, Dementia, Diabetes, Glaucoma, Tourette Syndrome, Depression and Insomnia to name a few. Furthermore an efficient and scientific based method / scheme involving the in-depth research, pre-

clinical studies and clinical trials) will go some way whether Medicinal Cannabis can be used as a therapeutic in these disorders.

3) What special considerations, if any, justify access to medicinal cannabis for:

(a) Patients who are under 18 years of age
(b) Patients who lack capacity by reason of age or another disability (other than youth) to consent to using medicinal cannabis?

There is the need to allow, under prescription issued by medical practitioners or specialised doctors, people under 18 to access medicinal cannabis and cannabis based drugs such as for regulated drugs already present in the market. Special consideration should be taken in the decision to prescribe patients under the age of 18 years of age with medicinal cannabis therapy. There following parameters should be assessed to determine the rationale for medicinal cannabis therapy:

i) Psychoactive side effect profile of the type of cannabis medicine prescribed
ii) Severity of the disease state in the patient
iii) Efficacy (or lack of) of other medications tried in the patient
iv) Have a definitive dosage, determined safety and efficacy profile of a cannabis medicine shown / demonstrated in clinical trials for the specific disease state
v) Potential for abuse
vi) Any contra indicatory conditions that the patient may suffer from, which may be severed by the cannabis medicine

Personality characterization should be conducted on the patient, and there should be strict monitoring on the amount of medicinal cannabis that is provided (weekly dispensing with accurate preparations of the dosing amount).

4) On which of the following should the law creating a medicinal cannabis scheme base a person's eligibility to use medicinal cannabis:
(a)a list of medical conditions
(b)a list of symptoms
(c)a list of symptoms arising from certain medical conditions
(d)evidence that all reasonable conventional treatments have been tried and failed?

There has to be condition-based categorization for the provision of Medical Cannabis therapy. Similar to the system proposed by the Medicinal Cannabis Scheme in Israel and Category 1 of Canada's Marihuana Medical Access Program, there has to be a list of disorders with their symptoms for which the Medicinal Cannabis treatment in permissible. Creating symptoms based models could possibly lead to exploitation and abuse of the system in order to get access to Medicinal Cannabis, and possibly lead

to complications as Medicinal Cannabis would not be a suitable therapy for the disorder. The American situation where medicinal cannabis and the various Compassionate Acts have been approved by the state governments is seen as a bridge to recreational use and regulation.

The access of Medicinal Cannabis should be purely reserved to a patient who has a disorder which is on the list of medical conditions approved by the Regulator as part of the medical cannabis access scheme. As mentioned before treatments with cannabis preparations must be prescribed by General Practitioners and supplied by pharmacies and hospitals, which should have the medicines in stock as such for already approved drugs. Regarding new conditions that may be treated with medical cannabis preparations and application from a Medical Practitioner specializing in that specific field, should be submitted to the regulatory committee or state agency in charge of medical cannabis regulation to be assessed for the treatment. By identifying target diseases, it can be easier to monitor and classify patients on the therapy and evaluate any pathological data that is generated. This data can contribute to an open-label clinical trial, or a study in which the efficacy can be determined. With this data, further legislation and planning will become easier and can follow easy logic on how effective Medicinal Cannabis really is.

5) Should there be a way to allow for special cases where a person who is otherwise ineligible may use medicinal cannabis? If so, what should that be?

Strict criterion and regulations need to be enforced to minimize the potential for abuse, or malpractice associated with Medicinal Cannabis therapy. To minimize the exploitation of the Scheme and avoid unintended recreational uses, there should be complete transparency from Medical Practitioners, who shall evaluate the condition and symptoms to permit a specific treatment and access a database where MDs / GPs can open a discussion in regard and exchange opinions with other doctors, patient community and regulators. Following a first evaluation, if there is a condition for which Medicinal Cannabis may be a potential treatment, a proposal must be submitted by the Medical Practitioner of the patient in question. This proposal will be reviewed by the Regulatory Committee and an initiation of a clinical trial should take place. The clinical trial should be open-label, and hence the medicinal cannabis can be compared to the other treatment options that are conventionally used for that disease.

In order to minimize these special cases, all diseases that have shown to have some evidence of being treated by Medicinal Cannabis (anecdotal or scientific) should be identified by the task force in charge of creating the classifications of use. Once all the diseases of interest have been identified, specialized networks for those diseases should be involved in the facilitation of clinical trials of cannabis-bases

preparations. Large networks of specialized physicians in a many different diseases should be involved, to ensure that the therapy is available to every patient that desperately requires it.

6) If Victoria acted through a state agency, in what circumstances would it be legally entitled to establish a medicinal cannabis scheme which `manufactured cannabis products without breaching the terms of the Therapeutic Drugs Act 1989 (Cth) or the Narcotic Drugs Act 1967 (Cth)?

According to Article 28.1 of the Narcotic Drugs Act 1967, the cultivation and production of cannabis resin is permitted to the guidelines stated in Article 23 are followed. Cannabis and opium have a lot in common, as they contain many compounds of therapeutic use and at the same time can be abused for their psychoactive properties. The whole idea behind Poppy cultivation for the production of opioids for clinical used, is to have stringent controls in place to make sure there is not illicit businesses are generated from the cultivation/production activity. Production of cannabis raw material must be for clinical purpose only, unless legislation modifications are enacted in the future.

If Victoria would like to act as a state agency or create a state agency, it could start the cultivation/production of cannabis medicines and stay within the legislation. As mentioned in Article 23.1-23.3 of the Narcotics Drugs Act, Victoria as a state agency would have to work in tandem with the party(s) in charge of cultivation and production with a rigorous deal of co-operation. According to 23.2.d:

"All cultivators of the opium poppy shall be required to deliver their total crops of opium to the Agency. The Agency shall purchase and take physical possession of such crops as soon as possible, but not later than four months after the end of the harvest."

If this law was then applied to the case of cannabis cultivation, the Victorian government would be solely responsible for the collection and distribution of cannabis as Botanical Raw Material (BRM). A highly secure venue could be chosen (preferably close to the cultivation site) where stocks of BRM and stored safely and at specific conditions (e.g. temperature, humidity, dark rooms, etc.) to minimise product deterioration (assessed through stability trials) (World Health Organisation 2003). The product could be then distributed to production site for the medicinal products, such as extraction and purification facilities that operate in GMP. Similar to how Bedrocan BV operates under contract to the Office of Medicinal Cannabis in the Netherlands, Victoria could open a state-licensed company, which runs through a government agency. However, a single entity is not advised, since it could create a monopolistic environment, which could slow down research and development of new drugs.

An easier way to operate within the terms of the Therapeutic Drugs Act of 1989 (Cth) is to initiate cultivation and production activities specifically for clinical trial purposes, under the clinical trial exemption scheme. In this manner, the medicinal form of cannabis can be given an "Exemption for special and experimental uses" as stated in Section 19 of the Therapeutic Goods Act 1989 (the Act). By initiating and open-label clinical trial in major hospitals for the conditions of interest, the Secretary of the Victorian Department of Health and Human Services could grant the approval of Medicinal Cannabis for clinical trials.

7) Are the regulatory objectives identified by the Commission appropriate? What changes, if any, would you make to them?

On the regulatory objectives identified by the Commission, our opinions on them are as followed:

"**Allow compassionately for exceptional circumstances of need"**

By allowing access to Medicinal Cannabis should not be viewed as an act of compassion, and should not be reserved for patients in exceptional circumstances. Acts of compassion, as seen in the USA, demonstrated that it could trigger a diverse use of these products, which most of the time tend to be rather for recreational use than for clinical use. Therefore Medicinal preparations of Cannabis should be viewed as a Medical Product that should be accessible to patients that fit the categorical requirements based on diseases not just symptoms. To ensure minimum abuse of the system, there shouldn't be any flexibility with regards to the categories that have been listed. If there is a condition that has not been identified by the commission (regulatory body in charge of listing the categories), then it should be proposed by a Medical Practitioner who specializes in the disorder in question to investigate Medicinal Cannabis therapy of the condition. Imposing a strict and foolproof model should be considered the only acceptable way for Regulating Medicinal Cannabis. It is very important to minimize thechances of finding 'loopholes'. Nonetheless access to Medicinal Cannabis should purely be Condition-Based, as it is regulated in Israel.

"Ensure that the use of medicinal cannabis is effectively integrated into the user's program of medical treatment"

The issue of integrating Medicinal Cannabis with other medical treatments is one that would be a case-by-case scenario. There would have to be considerations of the Drug-Drug interactions and possible

side effects from integrating different medications. These considerations need to be taken by the Patient's Medical Practitioner or by a Clinical Pharmacist or by a specialized MD.

In some cases like in drug resistant Paediatric Epilepsy, where Medicinal Cannabis has shown to be the only efficacious treatment, there wouldn't be the need to keep patients on other Anti-Epileptic Drugs (AEDs) that have little therapeutic effect but serious side-effects that impact considerably on the patient quality of life and state of living. Where Medicinal Cannabis provides a sufficient therapeutic value, one that is equal or better than other therapeutic drugs available, it should permissible to only be given Medicinal Cannabis.

However in other cases such as the treatment of nausea-induced by Chemotherapy, as well as opioid resistant Cancer pain, Medicinal Cannabis would have to be combined with cancer drugs (which are targeting the tumour). Even though there might be evidences suggesting that Medicinal Cannabis' present antitumor activity (Freimuth 2010), consideration has to be taken on how effective it is in blocking angiogenesis and slowing down cancer cell proliferation inducing them to apoptosis (Bifulco, Laezza et al. 2006, Guindon and Hohmann 2011, Hermanson and Marnett 2011). Therefore when designing categories of Medicinal Cannabis use, considerations should be taken on whether the Cannabis treatment should be integrated into the current treatment options, or whether it should be the sole treatment option for that condition.

"Ensure that informed consent is given to the use of medicinal cannabis and that there are not unacceptable side effects from its use"

Out of all the compounds present in Medicinal Cannabis, the only psychoactive compound is THC and other compounds derived from it. Even though THC causes unwanted psychotropic side effects, it also has evident therapeutic effects. Therefore preparations containing THC have to be closely monitored and controlled, and preparations with THC have to be labelled with advised considerations. The use of Medicinal Cannabis in the workplace would be dependent on the type of work performed, and the psychoactive profile of the cannabis preparation. Activities such as driving should not be taken place if the preparation is psychoactive and/or anxiolytic. Accurate and detailed labelling is therefore required for each Cannabis preparation.

"Ensure that medicinal cannabis is safe and of reliable quality and Composition"

The medicinal Cannabis preparation should be a medical grade product, and should undergo stringent analytical testing in all stages of production, packaging, storage and distribution. Strict validation, QC and QA procedures and protocols that are normally applied to products from the pharmaceutical industry are required to be applied in the manufacturing of drugs derived from cannabis. However it should not be only regulated the manufacturing of the finished drug product / formulation but the raw material require a quality management system as such for APIs of botanical origin (ICH 2010). Quality by designed should be built into both processes of upstream (cultivation) and downstream (purification) and dispensing. Moreover a continuous process verification and enhanced in-process analytics should be in place with the aim of monitoring repeatability of the process and consistency of the product.

The following list of guidelines should be followed in the production of Medicinal Cannabis:

- Good Agricultural Practice and Collection (GACP,World Health Organisation and ICH guidelines)
- Analytical Testing starting from what suggested by the American Herbal Pharmacopeia Cannabis compendium and possibly improved by the definition of experienced based local standards
- Current Good Manufacturing Practice (cGMP) for Active Pharmaceutical Ingredients, API (ICH)
- Validation of analytical procedures as set by the ICH
- Quality guidelines set by the Pharmaceutical cGMP regulations (FDA)
- Storage as per Good Storage Practices for Pharmaceuticals (World Health Organisation)
- Stability testing for API (World Health Organisation)

"Foster, and be responsive to, clinical research and advancements in Technology"

In order for Victoria to become a nationwide leader and prospectively a world leader in the area of cannabinoid science, it should engage different areas of academia by involving the top institutions of the country.

The following areas of academia can contribute significantly to worldwide research efforts:

1) Biomedical Research: enhance studies of the endocannabinoid system, investigations of its physiological role towards many different diseases and disorders. Look at the pharmacological

basis of all the active molecules in cannabis, and investigate the neurological effects of Cannabidiol and other cannabis derived molecules in treating Paediatric Epilepsy.

2) Botany research: involve botanical scientists who could develop more efficient agricultural systems for the production of higher quality Botanical Drug Material. They could also develop new genotypic and phenotypic selection of plants from seeds, depending on molecular characterisation, and the using cloning procedures or hybridization procedures to increase the levels of desired compounds. These clones of specific medical cannabis strains and hybrids could be sold to medicinal cannabis producers around the world.

3) Chemistry / Analytical Chemistry: explore and optimise the current extraction / fractionation / purification techniques; analytical techniques for detection of specific cannabinoids and other cannabis derived molecules such as terpenes, terpenoids and flavonoids. Design newer techniques and systems that could be more efficient and study the stability of the active molecules in the plant.

4) Engineering (Chemical / Biomedical / Biopharmaceutical / Mechatronics): develop efficient automated systems designed for mass scale production of Medical Grade Cannabis Products; creating incentives for a new industry for academics who chose to undertake these projects; improving current machinery for the analytical evaluation of the cannabis, and improving QA, QC and validation procedures and protocols.

5) Socio-Economics: analyse the sociological and economical effects of introducing Medicinal Cannabis treatments into society.

By creating University projects in these areas, many opportunities can arise for students to directly enter the Medicinal Cannabis industry. These University projects can be funded through the tax revenues generated through the sale of Medicinal Cannabis, or funded by private companies producing medicinal cannabis. Seminars and conferences can be held, inviting experts in this field of science from all over the world to hold seminars and workshops on various areas of the industry. Communication regarding the Medicinal Cannabis could be enhanced and people educated through educational school programs and conferences. This would make Victoria the worldwide hub of Cannabinoid Science.

"Enable the ongoing and effective enforcement of the prohibition on unauthorised cultivation, production, supply and use of cannabis"

There should be a presence of law enforcement to stop the unauthorised cultivators and producers of cannabis. Whoever wants to cultivate cannabis, must apply for a licence to produce Cannabis for Therapeutical purposes. The subject should be assessed for criminal records and authorisation should be evaluated by a government agency following a standard checklist. Other means of cultivation, e.g. for recreational purposes, should be enforced by law by giving heavy fines to subjects caught cultivating illegally based on quantity produced. Subjects caught should be penalized under the same legislation as they would be currently, and Medicinal Cannabis is not a product that can be produced by an untrained and unlicensed individual. However criminalisation is not the solution, so we suggest that heavy fines are better than to put people in jails.

8) Would the creation of a defence to prosecution for authorised patients and carers in possession of small amounts of dried cannabis or cannabis products be an adequate way of providing for people to be treated with medicinal cannabis in exceptional circumstances?

The whole purpose of the creation of the Medicinal Cannabis scheme should be so that there is a highly regulated program in which those patients, who require the product have access to the Medicinal Cannabis products, within the legal jurisdiction. The evidence showing the therapeutic effects of Medicinal Cannabis is substantial, and the legislation should be designed in order to guarantee a long-term goal of further developing therapies based on Cannabis.

The creation of a defence to prosecution does not reflect well on the greater goal in mind, which is to develop a sustainable platform from which the Medicinal Cannabis scheme can operate in Victoria. As mentioned in the response to Question 2, the medicinal effects of Cannabis are clearly evident. It has the ability to either replace or compliment current therapies and once more accurately defined, can the basis of future therapies. Therefore the defence to prosecution for authorised patients would not be a sustainable model for the long term outlook of Medicinal Cannabis. In order to provide the patients with the best available Medical Cannabis products, should be applied a wide scale Pharmaceutical System to its production to guarantee quality and safety of the product of botanical origin. By treating Medicinal Cannabis as a potential therapeutic substance and not a prohibited one, greater numbers of patients in need will be able to access a product of defined excellence produced following quality by design principles with state of art processes.

9) What mechanism should Victoria use to regulate the cultivation of medicinal cannabis?

The ideal method of cultivation of medicinal cannabis, is through a greenhouse horticulture system. Through this method of cultivation, ideal crops can be produced and it is the ideal way to attain consistency of the molecular content of the plant. The genetic strains should be chosen with relevance to targeted disease, as different strains have different molecular profiles. To reduce variability of the product mother plants with determined characteristics should be selected and cloned for reproducibility, since plants grown from seeds introduce genetic modifications and may incur in intrinsic variability from plant to plant.

As the Department of Environment and Primary Industries already has experience in the regulation of the industrial hemp industry, it could be given the task in regulating the GAPC guidelines (World Health Organization 2003). Industrial Hemp is very closely related to the strains proposed for medicinal cannabis, and it would not be very difficult to adapt the Standard Operating Procedures (SOPs) for medicinal cannabis.

To ensure that the medicinal cannabis is of Medical Grade Quality, Analytical testing practices such as GC and HPLC should be used to quantify the levels of active constituents, and therefore select the best fit for our upstream and downstream process (ICH 2005). GC and HPLC are also used in order to determine the peak harvest time. Batches of Botanical Raw Material (BRM) should be tested using composite sampling techniques as described in "Botanicals: Methods and Techniques for Quality & Authenticity" (Reynertson and Mahmood 2015). The approximate timeframe for production of the BRM is 3/4 months depending on the strain, and therefore the body which has been assigned for analytic testing should conducting the testing at the time of harvest. Furthermore, in order to monitor quality of the product a continuous process verification system during cultivation process should be in place. This mainly concerns a defined protocol of an in-process testing of botanical raw material during flowering period with randomised sampling to control contaminants levels, and traceability must be recorded regularly in batch process sheets (batch records). Visual inspection is also important to monitor presence of insects and fungi that may affect the quality of the batch.

The molecular profile of the harvested BRM should be analysed with a complete characterisation to ensure that a measure of consistency is attained. The BRM should also be analysed to make for the levels of contaminants such as Pesticides, Heavy Metals and Microbiological Contaminants. Once the harvest is complete at the optimal time, the inflorescences should be packaged according to Good Storage Guidelines for pharmaceuticals (World Health Organisation 2003), and in lieu of

Microbiological Quality Practices (European Pharmacopeia) in order to prevent contaminations (European Directorate for the Quality of Medicines 2007). These guidelines are part and parcel of treating Medicinal Cannabis or Cannabis-based medicines like Medical Grade products of botanical origin. Composite sampling should also be conducted, to ensure there is variability caused by the packaging procedures.

The responsibility of analytical testing could be given to a Government organisation such as CSIRO, or BIO21 or other, perhaps private companies who specialize in analytic testing for agriculture purposes (through third party authorization to avoid conflict of interest).

10) What approach, or approaches, should Victoria take to regulating how medicinal cannabis is processed and distributed?

There should be a Processing License Scheme for companies involved in the production of Medicinal Cannabis products, under which they are operating under strict regulations. They will be obliged to run procedures under strict regulations, especially if they are dealing with psychoactive compounds. They will have to operate with complete transparency, especially when showing the numbers of products generated out of the harvested Botanical Raw Material (BRM). There should be regular reporting of the BRM in the area cultivated, reports on the quantities as well as the reports on the loss or failure of the plants for traceability purposes and batch records must be written for the purpose. This has to be done to ensure that there is not malpractice associated within the production line, which could be subject to further legal complications. The company should be set up for regular audits in all these areas, and possibly outsource this to independent contractors who are experienced in conducted audits on BRM (from poppy industry).

Companies that are involved in the processing of Medicinal Cannabis should be regulated with an overriding Quality Management System, which is enforced by the Victorian Regulatory commission. This has to be done in order to attain Medicinal Cannabis which adheres to its quality characteristics e.g. identity, strength and purity. There should be Quality Control Units present in each company, as well as a Victorian Medicinal Cannabis Quality Control Unit which ensures that cGMP regulations are being followed rigorously and make sure that the Medicinal products are adequately suitable for treating patients (Food and Drug Administration 2006, Therapeutic Goods Administration 2009).

As the constituents of cannabis are active and subject to stability issues, there has to be an application of procedures which are model around the product which is being distributed. Every Medicinal Cannabis products would have separate storage requirements and expiry dates, and they have to be considered when they are distributed to sites of dispensation or administration. Pharmaceutical products have guidelines set for distribution, and the *WHO good distribution practices for pharmaceutical products* is a good model for this purpose (World Health Organization 2012). Using this guideline as a guideline, Standard Operating Procedures (SOPs) could be developed for the distribution of specific Medicinal Cannabis products by the Victorian Regulatory Commission. These SOPs can then be passed on to other states which might adopt the same model in the future.

11) How should the Victorian medicinal cannabis scheme interact with the national arrangements for the control of therapeutic products under therapeutic goods legislation and narcotic drugs legislation?

Victoria's medicinal cannabis scheme should start by initiating clinical trials on Medicinal Cannabis. Open-Label Clinical trials should be conducted on extracts and formulations of Medicinal Cannabis, and not on raw cannabis inflorescences (flowers). With extracts there is the ability to have greater control on the dosage, administration and quality of the Medicinal Cannabis product. There are extraction techniques such as CO_2 supercritical extraction, that have the capability to remove certain compounds selectively, such as THC, which might be contra-indicatory for the age of the patients at a concentration that is higher than the psychoactive threshold or to certain disorder (in the case of epileptic conditions, THC has shown to be pro-convulsive). Through chromatographic separation techniques (e.g. affinity chromatography) the levels of specific compounds can be tailored to the target disease. All diseases that might be potentially treated with Medicinal Cannabis should be identified, and clinical trials should be conducted in major hospitals, headed by specialized medical practitioners in the field.

The Open-Label clinical trials of Medicinal Cannabis extracts can fall under the Clinical Trials Exemption Scheme (CTX), which grants the clinical investigational use of a product which is not registered on the Australian Register of Therapeutic Goods. However Victoria does not need to import a medicinal cannabis product, as it can stay within the regulation by cultivating and produce the product within the state. Abiding by the *Narcotic Drugs Act of 1967*, it can issue State-licenses or be directly involved in the cultivation and manufacture of Medicinal Cannabis. This would not be prohibited by the Commonwealth Criminal Code and through vertical integration, it would be easier for the State regulatory committees to monitor production.

The rationale for conducting clinical trials is simple. It would be a huge step in clarifying the efficacy of cannabis-based products for different diseases, and would therefore provide a better basis to grant further approval from Federal Lawmakers and the Medical Community in Australia. Cannabis-based preparations would vary from disease to disease, and hence they should be registered separately on the Australian Register of Therapeutic Goods. Conducting large-scale clinical trials, with concurrent pre-clinical studies will also contribute to demystifying the scientific basis for using cannabis-based preparations.

In conclusion, Victoria should initiate a fully state orientated scheme in which there is direct regulatory control over all aspects. This ranges from the cultivation, development of the products to the administration and monitoring of patients in the clinical trials.

12) What responsibilities should be given to health practitioners in authorising a patient's use of medicinal cannabis?

Regardless whether the final regulations authorise a specialist medical professional to prescribe medicinal cannabis preparations or if they are required to submit a request to a regulatory committee, they will have to accept certain responsibilities as they will be the link between the research and medical care.

Like all medical decisions, the choice to receive Medicinal Cannabis must be based on the informed consent of the patient, or their legal guardian should the patient not be able to take a decision on its own. This will require the full disclosure about potential benefits and harms of the specific cannabis preparation and an explanation of what the participation in the open label clinical trial entails.

The medical specialist will be required to continuously keep up with any emerging results and information, and should there be an indication that may require modification or termination of the treatment of the disease involved actions should be taken immediately.

The authorising health practitioner will need to ensure that all relevant medical professionals involved in the medical care of a patient, including pharmacists and other health care workers, are notified about the treatment and stand in continuing communication with each other. This will ensure that the preparation does not interfere with any other treatments, including treatments for unrelated diseases, and allow for patients to be rigorously monitored for potential side effects.

There should be an especially close cooperation with the general physician, who will have a key role in symptom surveillance, as they will be seeing patients on the most frequent basis and are therefore better suited to put in place previously mentioned tools, including symptom diaries. All findings will need to be passed on to the specialist on a regular basis and the specialist should be immediately notified if there are any concerns.

Further the authorising health practitioner will be required to cooperate with the general practitioner to ensure that any limitations which may be set for a specific cannabis preparation including driving and operating heavy machinery are upheld to ensure the safety of the general public. Care should be taken however to uphold Patient confidentiality, as the treatment with cannabis derived medications may cause patients to experience a negative social stigma.

Finally should the cannabis preparation include THC, the authorising health practitioner is responsible to ensure that the patients mental health is assessed frequently for any changes including but not limited to early signs of schizophrenia and anxiety disorders. We recommend that mental health monitoring guidelines are put into place for these medications, at least until more data has been analysed.

13) Who should have the authority to assess whether a patient is an appropriate candidate to be treated with medicinal cannabis?

(a) all registered medical practitioners
(b) certain designated specialist medical practitioners
(c) registered health practitioners who have prescribing entitlements
(d) a subset of these?

As previously mentioned, to be considered for Medicinal Cannabis, a patient will have to be diagnosed with a disease that has been approved for a specific cannabis preparation. This authorisation comes from the regulatory committee itself or a body within the regulatory committee depending on final regulation.

Therefore only health practitioners who are specialists in the specific disease field, positions defined by the regulatory committee, will have the authority to assess and potentially apply for medicinal cannabis preparations.

For example, a paediatric neurologist will be able to assess the suitability of a child with intractable epilepsy. The rationale is that the assessing health practitioner requires an intimate knowledge of the disease, the current treatments for that disease and how effective those treatment have been for the

patient in question. This is the only way to ensure that they are able to make the best possible decision for the patient's wellbeing.

14) What requirements, restrictions, guidance or other assistance should Health practitioners be given in monitoring a patient's use of medicinal cannabis?

A key part of the Medicinal Cannabis Scheme will be the reliable collection of data, enabling effective monitoring and evaluation of symptom improvement, disease progression and side effects.

As the data collection will be undertaken by different practitioners the aim will be to develop tools allowing for a uniform and unbiased collection of the data. This will be achieved through strict monitoring protocols, which will include all examinations and investigations as well as their respective time intervals. Development will be done by a multidisciplinary team, ensuring that the desired results are achievable in clinical practice.

The protocols will be specific for each cannabis containing preparation they simultaneously provide a way to strictly monitor individual side effects. In the case of THC containing preparations for example, mental health monitoring protocols will be included.

Further a network of communication will need to be implemented in order to provide reliable transmission of data between the health practitioner and the agency in charge of collecting and distributing the data. A central medicinal cannabis database should be created for the purpose of collecting and sharing (patient will be coded anonymously) data and information. Health practitioners will be given training and instructions on this process to ensure a working flow of information.

We hope to address the issue of potential medicinal cannabis preparation abuse by stringent disease based categorisation and by the use of low dose preparations, specifically designed for each disease. However acknowledging that high levels of care should be taken, quantity restrictions for cannabis preparations should apply and information should be provided to all health practitioners directly involved with the patient to ensure that they all have knowledge of the signs of potential medication abuse.

This will include self-administration of the medication through unintended routes, administration of increased quantity and selling of medications to third parties.

Under the proposed regulation, 'Doctor Shopping', an issue that is prevalent in other states that have legalised medical cannabis will not be a problem. 'Doctor Shopping' is the process whereby patients frequent multiple health practitioners until they receive a prescription for medical cannabis.
The utilisation of condition based inclusion criteria, development of medications that are free of the effect sought after by recreational cannabis users and only authorising disease specialists to assess eligibility will ensure that only patients who may benefit medically are included.

15) What additional restrictions or requirements, if any, should apply to patients who are vulnerable by reason of age or lack of capacity, so as to provide adequate protection for their welfare?

Some of the disorders which are considered for treatment with Medicinal Cannabis may deal with diminished mental capacity, and hence they may not have the legal competence to reason or deliberate about the treatment they wish to receive (Berg, Appelbam et al. 1996). Neurological disorders particularly fit into this category e.g. Paediatric Epilepsy and Alzheimer's disease, as well as some other conditions for which Medicinal Cannabis treatment is being proposed for e.g. Palliative Care. Therefore the issue of medical consent in these cases is of great importance, and one that should be ensured to avoid any potential medical malpractice.

When the patient is in a state of diminished mental capacity, and is unable to make his/her own decisions regarding their medical treatment, the Guardianship and Administration Act 1986 (Vic) identifies a list of decision makers who can act to give the patient's legal consent. This is the case for any medical treatment in these conditions and hence the same practice should be applied to Medicinal Cannabis. The Medical Practitioner of patient should have adequate understanding that the patient fits into the category of the approved treatment schedules of Medicinal Cannabis, which are developed based on the evidence of the efficacy of Medicinal Cannabis for set treatment (as discussed in the response to Question 2).

At the same time, the decision maker with the legal consent of patient with diminished mental capacity should be able to refuse the Medicinal Cannabis treatment even if it is highly recommended by the patient's Medical Practitioner. This ability is covered by the The Medical Treatment Act 1988 (Vic), which clarifies the right for people to refuse medical treatment. Even though this may be contradictory to the patient's well-being, Medicinal Cannabis should be treated like a conventional Medical Treatment to ensure that there is a foolproof and legally consistent model.

16) In what form(s) should medicinal cannabis be permitted to be supplied and used?

Cannabis cannot be treated a single entity. It is a highly variable substance, with over 90 compounds that have shown to have some pharmacological activity. The cannabinoids are the class of compounds that are commonly associated with cannabis, and each of them have shown to have different affects at the cellular level. They are not all associated with the same target receptors and proteins, and some of them have shown to have opposing effects e.g. THC is a partial agonist at CB1 and CB2, while CBD is an antagonist and inverse agonist at CB1 and CB2 respectively (Thomas, Baillie et al. 2007, Pertwee 2008). Besides from the cannabinoids there are many other classes of compounds in cannabis such as the terpenes, flavonoids, alkaloids, amides and lignamides. Even though some of the compounds are only present in small amounts compared to the dominant cannabinoids, they might contribute to some synergistic activity.

In order to define the type of medicinal cannabis required for each product, there is a necessity to designate the molecules as per there target receptors and cellular proteins. The best way to do this is to create extracts of cannabis, which can then proceed to molecular characterization. By isolating specific molecules for specific diseases, these molecules can be separated through chromatographic methods and re-formulated into medicines for the disease in question. By supplying cannabis formulations, the control and stability of the molecular content can be more rigorous than if the inflorescences were supplied. Inflorescences can undergo transformation over time, which could be detrimental to the patient administering it. It can be easier to control the dosage in a formulated preparation, and the route of administration can be simplified (oral administration).

Looking into the long term development of the Medicinal Cannabis scheme, multiple Pharmaceutical Preparations should be in the pipeline. By varying the levels of the cannabinoids with respect to each condition, more clinical as well as scientific knowledge can be attained from scheme. This detail of variability cannot be attained by through the administration of purely Cannabis plant inflorescence, as the stability of molecules changes drastically in the plant.

17) In what ways could Victoria's medicinal cannabis scheme keep pace with, and contribute to, clinical research into the therapeutic uses of cannabis and other changes in scientific knowledge, medical practices and technology?

There has to be a rigorous approach taken with regards to the monitoring of Medicinal Cannabis Patients. Researchers, medical practitioners and regulators will contribute to closely studying any outcomes

(desirable or non-desirable) that might have been attained from usage of cannabis-based Medicinal Products.

There has to be regular interaction of the patients with their Medical Practitioners for this purpose. Regular diaries of symptom surveillance must be written, and if the treatment is successful to reduce the symptoms –there should accurate notification. Same for unexpected side-effects, the patient or the carer or the medical practitioner should accurately notify any adverse event. In order for there to be the assessment of tolerance and safety (Lachenmeier and Rehm 2015) or side effects over the long-term, this assessment has to be performed over a period of at least 3-4 months for any accurate conclusions about the efficacy of the treatment. Therefore any changes to the scheme can be made immediately, as results should be interpreted and review by a separate Medical Regulatory Committee. The best and most regulated way to conduct all these medical practices would be under the operation of multi-centre open-label clinical trials. Patients in dire need of the treatment would be able to access it, assuming they fit the required Condition requirements, and there would be a structure for the surveillance to take place.

Multiple University research groups and Research Institutes should be involved into looking into the various properties of the plant. Research projects could be started to study the chemical analysis, analysis of the active compounds present and technologies related to the development of Medical-Grade Cannabis products. Institutes that deal with Botany research, Pharmacological research, Pharmaceutical development, Pharmaceutical Engineering, Plant Chemistry, Human Physiology and most importantly Social Science should be involved with Victoria's Medical Cannabis Scheme. By involving experts from a wide array of disciplines, there can be a wide-scale initiative for technological and scientific advancement in this area.

University courses could offer specialized pathways in this area of science, which would foster the future development of expertise in this field. Innovation will be assured and the State of Victoria could be on the forefront on a field that is attracting worldwide interest. Victoria can a have an extremely large role to play, and would have the opportunity to enhance its worldwide reputation as a hub of Biomedical Research. Initially, there would be a requirement of involving a number of foreign institutions already involved in the relevant areas of research and development. Training programs and workshops could be conducted to train current and future experts in this field. Some of these institutions have strong bonds with Australian Institutions, and these bonds would only become stronger with prosperous collaborations.

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