2 April 2015

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Senate Legal and Constitutional Affairs Legislation Committee
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Re: Inquiry into the Regulator of Medicinal Cannabis Bill 2014

We hereby wish to submit an inquiry to the Australian Government and all relevant bodies to support the "Regulator of Medical Cannabis Bill 2014". We wish to acknowledge that the newly established working group for research on medicinal cannabis, the European Network for Research on Therapeutical Cannabis, supports the "Regulator of Medicinal Cannabis Bill 2014". The group, represented by the secretary Sergio Pagliazzi, Pharmaceutical Engineer, and President Professor Umberto Veronesi, former Italian Ministry of Health, is strongly convinced of the importance of properly regulating access and research concerning products derived from cannabis. As well as this group, Professor Terence John O'Brien (The James Stewart Chair of Medicine and Head of the Department of Medicine, The Royal Melbourne and Western Hospital, at The University of Melbourne) and Dr Tina Soulis (General Manager at Neuroscience Trials Australia) also wish to present their support to this bill. We are supporting the proposal for a legislative change because there is a need to clearly evaluate clinical uses by pursuing clinical studies that comply with Good Clinical Practice regulations, given the promising pharmacological activities of the active compounds of the plant, shown by a tremendous increase in scientific publications as well as the overriding anecdotal evidence coming from the USA.

Following a worldwide change in opinions regarding the use of medical cannabis, we agree with the proposed bill by stating that there is an absolute need to create a lawful regulatory environment that will help innovation through the application of pharmaceutical systems that guarantee the quality of the raw product and the subsequent process of extraction / purification abiding by the Active Pharmaceutical Ingredients (API) [1] regulations. It is necessary to evaluate the therapeutic efficacy and safety, at the same time, demonstrating the lack of side effects; define the standard dosage of the product and the most appropriate delivery method to be used for clinical testing and for the treatments required by patients (e.g. syrups, tablets, infusions, oils, creams). Currently, the awareness of the effectiveness and the low levels of addiction (in contrast to opioids) is based mostly only on the pre-clinical evidence reported in the international scientific literature. There is evidence of the therapeutic effects from both in vitro and in vivo models of disease, as well as from the feedback of patients that use the substance in US and other countries. Provision is through dispensaries or pharmacies (USA, Italy) with, in some cases, users turning to the illegal market to access the product.

Nonetheless, there is a clear need for multiple clinical campaigns with the aims of investigating the clinical effects of cannabis-based medicines by addressing target diseases. Therefore, universities and research centers should be involved by conducting research to explore the pharmacological effects of the psychoactive compounds in cannabis and to increase the specific knowledge regarding the role of the endocannabinoid system, which is considered to have a definitive control in the causes of neurological diseases and cellular development.

We agree on the fact that there must be a register of regulated medicinal cannabis products. However as suggested by the 1961 Convention on Narcotic Drugs, there must be a government body for the purpose that not only issues licenses but also routinely controls documentation to fulfil principles of good practise. Differently from the model proposed by the 1961 Convention, in which they compare cultivation and regulation of opium poppies and intend to limit the applications for licenses only to public companies, we believe that private companies should be involved and contribute, through private investments, to research and development of cannabis derived drugs. This competition will enhance innovation and help Australia to become leader of cannabis-based research and contribute in improving the evidence baseline of cannabis derived products. This matter should be discussed at the 2016 Convention on Narcotic Drugs as well as the permit of international trade of medical cannabis for therapeutic purposes that will enable international technology transfer from countries with expertise in cannabis research or in which research is allowed by local legislation such as: Israel, USA, Italy, Netherlands, Uruguay and Spain. This will make it feasible to trade Botanical Raw Material (BRM) for pharmaceutical development purposes and for the development and trade of quality standards kits to measure specific contaminants levels as well as cannabinoid profiles (e.g. exportation of quality standards of cannabis is currently not allowed by the US federal government).

Strict rules should be applied regarding the application of Good Agricultural Practices GAP [2] and ICH guideline for Active Pharmaceutical Ingredients [1] for traceability purpose and for production of medical grade quality cannabis-based products. Standards Australia should be involved in the definition of such national regulation. A cultivation scheme or general protocol should be provided as a guideline for interested parties since Active Pharmaceutical Ingredients (APIs) derived from botanical origin must comply with defined quality attributes requirements as explained for example in the American Pharmacopeia for Herbal Medicines (Cannabis) [3]. However, the regulator may think about involving international experts to write a local pharmacopeia in regards to cannabis regulation. A Government body or a private company should be created and must be in charge of certifying and routinely inspect that a person or a company comply with the method of cultivation according to regulation. Possibly, a government owned laboratory should test the botanical raw material to allow its final release in the market as approved BRM for clinical purposes. The extraction steps should be regulated as per production of nutraceutical or pharmaceutical drugs by complying with Good Manufacturing Practise (GMP) [4] principles.

Nonetheless the bill should control the use of cannabis and extracts and determine its specific clinical use without incurring legislative misunderstandings that may induce the public to seek different uses of the products, and not for clinical purposes. Traceability and documentation according to the above mentioned guidelines should help defining product characteristics and ensuring that the produced raw material should not be redirected to the illegal market for recreational purposes. Moreover the Government should think about a concurrent educational scheme that should be introduced in schools from the moment the bill will be approved in order to teach young people about the pros and cons

of cannabis use, that it should be restricted to clinical purposes. People shall be informed about effects, mode of use and dosage and the product shall be presented as a medicine and evaluated for its clinical and pharmacological properties. It is important to define Cannabis as a medicinal product and not a recreational one, and one that should not be used without the recommendation of a physician.

As such, the goal must be to proceed through the application of the rules of good scientific practise, defining the correct dosage, utilise statistical means to demonstrate safety and effectiveness and analyse possible but unlikely side effects of these treatments. Currently the major cases of interest are childhood epilepsy, neurodegenerative diseases, cancer, glaucoma, AIDS, palliative care and the treatment of chronic pain. Because of a specific market analysis of the demand for medical cannabis by patients, it appears that the licensing and authorisation required to fulfil this demand should not be limited to few entities. It should be available to a wide group of private and public institutions such as interested private companies, research institutes and universities with the aim to cover the procurement of the number of patients defined by epidemiology studies in order to produce the raw material necessary for scientific research. Medicinal Cannabis Therapy of 60-90 days may require an amount of 200 grams of botanical raw material per year per patient taking into account diseases treatable by medical cannabis. Annexed to this submission is a brief introduction on the company, UTT BioPharmaceuticals. It is an Italian-based entity, which also intends to open up a partner institution in Australia and aims to operate in concordance with its collaborators based in Australia. Short summaries of our opinions regarding the few issues concerning medicinal cannabis are also annexed to this submission.

We support with great interest the opening of the legislation Australian Government is pursuing to the therapeutic use of cannabis and we are grateful for the opportunity to comment. Regarding, UTT BioPharmaceuticals, we are welcome to reveal the Operating Plan specifically designed for Australia in a transparent fashion. For further information please contact Sergio Pagliazzi

Yours sincerely,

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ANNEX 1: Our input on the few issues regarding Medicinal Cannabis.

Quality control and quality assurance of botanical raw materials

The absolute requirement for a plant-based medicine from a regulatory point of view is the control of raw materials. During its manufacturing process, a drug goes through many processes, each of which must be monitored and exceed quality controls. Quality standards will be invalidated if the raw materials, such as materials of botanical origin, are of poor quality or inconsistent. The consistency of the botanical product cultivated or manufactured is of primary importance in order to establish a baseline for clinical studies, which must show statistical relevance.

Laboratory analysis of plant lines of selected origin needs to show that the ratios of cannabinoids and other molecules are very consistent during the cultivation and that contaminants levels (e.g. heavy metals, pesticides and herbicides) are below the allowable limit defined by regulation. The consistency of the product is monitored by the characterization of the product that defines the level of the various contaminants and how to be stay within the permitted levels of endotoxins, mycotoxins, contaminating molecules, the presence of insects, fungi, pesticides and herbicides following the guidelines of the American Pharmacopeia for agricultural production [3]. The quality system will consist of a continuous verification of the production process, qualitative and quantitative analysis, to monitor and optimize the yield of the manufacturing process. This will surely increase production cost but at the same time ensures that the patients and institutions concerned have access to a certified product that can be considered of Active Pharmaceutical Ingredient grade. Such high levels of consistency are unusual in plants and are very important in new applications for approval of the drug made to the regulatory authorities, such as the TGA.

Therefore, we propose to cultivate the plant material, extraction and formulation in dosage forms of the cannabinoids and other pharmacologically active components from the plant in fully automated and controlled environments as applied to pharmaceutical companies. Each step should be carefully controlled by following guidelines issued by regulatory bodies and ICH (International Conference for Harmonization), which obliges all drug manufacturers to follow the procedures of quality-controlled and subject to the same stringent standard operations (SOP) and protocols [5]. Compliance with these standards and regulations should be carefully monitored by national regulatory agencies such as the Ministry of Health or an ad hoc agency.

The intention of authorised farmers or companies should be to use the material of the cannabis plant exclusively for developing their cannabis-based nutraceutical/pharmaceutical products and supply companies or laboratories for research purposes. Providers should not distribute herbal cannabis to the public but to researchers or clinicians. The products manufactured should be safe and effective for a particular disease; manufactured in accordance with the processes of quality control and validation; highly standardized and consistent from batch to batch; provide a fixed dose and reproducibility; and that could be reimbursed by the patient's health insurance program or through Medicare scheme.

Case study: Paediatric Epilepsy desperate need for controlled clinical trials

There is a mix of pre-clinical experimental and anecdotal data suggests the role of the endocannabinoid system in the treatment of sub-types of epilepsy. The two types of Paediatric Epilepsy that have shown to be relevant in this case are Dravet and Lennox-Gasteut syndromes. From pre-clinical studies seems that cannabinoids have a major role in both the pro-convulsion (which cause seizures) as well as the anti-convulsion (which reduce seizures). The cannabinoid of interest is cannabidiol (CBD) which is thought to be the main component leading to the anti-convulsive effects of cannabis. CBD-enriched cannabis has shown to have significant efficacy against epilepsy in human subjects [6] and there are a number of well-documented cases from around the world, such as the case of Charlotte Figi, which have shown CBD's effectiveness. This is keeping in mind the fact that no other drugs had any therapeutic effect on Charlotte, and only a strain of cannabis with high levels of CBD was effective in helping her condition.

Due to the lack of side effects of shown by CBD [6], clinical studies can be fast-tracked and can directly proceed to Phase II clinical trials for epileptic patients suffering from AED resistant epilepsy. However CBD may not be the only component of medical cannabis with anticonvulsant properties or therapeutic potential with regards to treating patients with AED resistant epilepsy. There are other active compounds present in the cannabis plant that have shown to anticonvulsant properties such as Δ^9- tetrahydrocannabivarin (Δ^9-THCV) [7], cannabidivarin (CBDV) [8], and Linalool [9]. Along with other anticonvulsant compounds, there are many compounds that may have additional beneficial effects for patients e.g. Nerolidol(sedative) [10], β-Myrcene (analgesic and muscle relaxant) [11] and Limonene (anxiolytic) [12], cannabinol (CBN) (sedative) [13] and cannabichromene (analgesic and anti-depressant) [14]. These compounds with their beneficial characteristics can be extremely helpful in improving the quality of life of patients and could potentially be delivered in combination with the anticonvulsants. A lot is to be known about the therapeutic potential of medical cannabis and its constituents, and the maximal benefit one can attain from it.

It is essential that there is more research conducted into exactly why CBD is effective against Dravet and Lennox-Gasteut syndromes. Even though several hypotheses have been proposed, there is still a lot to be found out in this area of science. Many physicians and scientists in Australia have shown a great deal of interest in trialling a CBD-based product for these diseases, and investigating their effects from a pharmacological point of view.

Educative school programs

In order to support the growing demands on the part of patients, associations, institutions and doctors there must be a full commitment to establish educative programs on the effects of cannabis and its derivatives. As cannabis is a drug that can be abused, and has the capability of causing psychological disorders and anti-social behaviour when THC is administered at high dosages, a countrywide initiative to educate the next generation would be required. It would be necessary to distinguish the medicinal components of cannabis, with the psychoactive components and convey this information to the general public.

This could be an opportunity to fit into a global context and contribute communicating issues on cannabis or extracts which will help the medical context and try to educate people on its controlled use. Educational and drug prevention efforts could be funded from revenues raised from taxing cannabis-based medicinal products, and therefore they would not present an extra financial burden on the Government. By treating abuse and addiction as a psychological issue rather than a criminal one, it can help eradicate this problem from a societal standpoint.

Security of Medicinal Products

As cannabis has the potential to be a drug of abuse, the sites associated with the development of cannabis-based medicines would attract the attention of criminal groups. These sites would include the cultivation areas, manufacturing plants for cannabis-based medicines, storage and dispensing sites. In order for there to be stringent control on the products, that only those in need should be able to access it, it would require full transparency from the authorized producers. Regular involvement of government appointed regulators would be required at all levels at which cannabis products are available, especially for the monitoring of the harvested cannabis inflorescences and have complete assurance that the entire harvested crop is being involved in the manufacturing steps.

A good example on how the security of the crops and downstream products can be maintained is by following the same framework that is applied to the production of poppy-based products in Tasmania. Poppy is similar to cannabis, as it can be a potential drug of abuse but it clearly has components of great therapeutic interest. Appendices 4-10 of the "Review of the Tasmanian Poppy Industry Regulation" conducted by John Ramsey & Associates provide a good reference point [15]. They outline the steps that can be taken to ensure that there are no theft malpractices that may arise from Medicinal Cannabis cultivation and production.

Annex 2: UTT BioPharmaceuticals LLC

UTT BioPharmaceuticals LLC

In order to provide the medical-grade pharmaceutical cannabis products, UTT BioPharmaceuticals would be able to fulfil this requirement. It has put together experienced personnel in the aspects of pharmaceutical production, drug discovery and clinical trial management. It is affiliated with a network of associations and research institutes that support the idea of experimenting with cannabis derivatives for the treatment of diseases neurological, cancer, nausea induced by chemotherapy and radiation therapy, pain and epilepsy to name a few. There is growing awareness of the effectiveness of extracts from cannabis for the treatment of epilepsy, chronic pain and other conditions, but it is mostly based on the anecdotal feedback of patients who use the substance illegally or access it through dispensaries (licensed pharmacies) where it is legal.

The research and the development of substances for medical use is the focus of the project, given the possibility of developing drugs with different characteristics from similar drugs present in the market today supported by the accessibility to a wide variety of active molecules contained in cannabis crude (inflorescences and residues on the plant). The cannabis plant holds an immense potential for treating many other disorders and diseases mentioned previously, and UTT aims to explore these possibilities and create a product pipeline of medicines.

In a time of economic crisis like the present there has been a change of direction in public institutions, largely due to pressure from the medical community as well as patients in dire need. This is demonstrated by the widespread discussions on authorization and licensing of cannabis cultivation in Europe and USA, which represent a clear opening to the topic. An example of pilot program has been started in Italy through the authorization granted to the Chemical-Pharmaceutical Military Plant in Florence. In this context, companies are organizing to create and define this emerging market that will guarantee profits to reinvest in medical research and innovation. Access to new revenue is guaranteed by the possibility of taxing the various medicinal products cannabis, currently under the control of black market and the mafia, and this would be of great economic benefit. By reinvesting this revenue into healthcare, citizens will be reduced of the tax burden of medical costs. It will present the opportunity to help and clinically treat patients who actually require these types of products that are currently very difficult to access.

The opportunity is to create, with the support of the medical community and in agreement with the Regulator, an Australian partner institution to a company in Italy that can fit into a context of the international market with the ability to be a leader thanks to technology and operational dynamics. The goal is to enter a market valued at € 1 billion, in

constant development and great growth potential, with capacity for rapid growth comparable only to the market of smartphones (Apple Corp. is currently the industry leader and number one in the world market capital). With the help of investors, research institutes and medical experts, the team is willing to get involved and take up this opportunity. This will be accomplished by following a plan for medium and long term to turn the opportunity into a success.

We have described a chronological road-to-market framework in Europe and Australia, in order to fund research and development in order to support the achievement of the ultimate goal. This is namely to define new therapies based on cannabis products developed with the aim of commercializing a low-cost product, for diseases that affect the quality of life of patients and weigh heavily on the national health care system because of the high costs of the therapies used today.

UTT BioPharmaceuticals wants to be ahead of the times. We want to define the properties of compounds of medical cannabis on a scientific basis and support the changes of legislation. The goal of UTT BioPharmaceuticals is to support not only the development of drugs to help patients, but to support the legalization of medical cannabis to patients. We aim to make a controlled product in the short term that could be distributed to licensed pharmacies. The idea is associated with the possibility of re-directing part of the product to research centers affiliated at a subsidized cost, in exchange for their help in cannabis research.

This way UTT BioPharmaceuticals intends to position itself as a supplier of crude extracts for therapeutic use, which will be cultivated by extracting the active content by following GAP (Good Agricultural Practices) [2] and GMP (Good Manufacturing Practice) [4]. The raw material and extracts of botanical origin for medical use will be stored as per TGA [9] guidelines and highly controlled. The dispensed drugs in the form of medicines will reach the public through the National Health Service, which could deal with the distribution.

UTT is committed to establish a network of experts in various sectors that supports the project. With distinct opinions received from patients, patient associations, research institutes, hospitals experts we could represent the different strategic scenarios. This framework will provide extracts that are more or less pure, for example oil-based for patients that require immediate use and to be used in clinical trials diversified, as requested by research centers and patient associations. Our scientific advisors are members of institutes or members of associations such as University of Pavia, IEO (European Oncology Institute), Veronesi Foundation, Royal Melbourne Hospital, Florey Institute, FIE (Italian Epilepsy Federation), ILAE (International League Against Epilepsy) that are interested in deepen studies concerning the use of cannabis derivatives for the treatment of epilepsy, muscle spasms and spasticity in MS and ALS, for the treatment of pain p, palliative care and cancer research as well as the neuroprotective function of cannabis.

In Australia, UTT has a collaboration with the Australian Epilepsy Clinical Trial Network (AECTN), which is a professional network of academic epilepsy centres and is a group within the Epilepsy Society of Australia (ESA). They work in a partnership with Neuroscience Trials Australia (NTA), which is an Australian based Contract Research Organisation (CRO) specializing in neuroscience clinical research. With an average of 14 years industry experience, the AECTN-NTA partnership has staff with global management expertise in all phases of clinical research including studies sponsored by pharmaceutical and device companies, the biotechnology industry, granting bodies (such as the NIH or Australian equivalent NHMRC), collaborative groups, institutions and investigator-initiated studies. In this collaboration, UTT will be the supplier of cannabis-based medicines of the intended clinical trials run by the AECTN-NTA partnership.

An expression of interest has already been submitted to conduct clinical trials on Paediatric Epilepsy, for the NSW Government Sponsored clinical trials expected to take place in 2016. This collaborative effort hopes to conduct similar clinical trials in the other states of Australia, and has a great deal of expertise to do so.

In any case, the main idea is to get permission to grow cannabis sativa, indica or hybrids without limiting the molecular content of the plant. We shall work toward selecting ad hoc strains and standardizing the quality of the product by reducing the variability due to the evolution of the seed using genetic cloning methods and QC, QA and validation protocols as a part of the manufacturing process.

UTT does not intend to restrict itself to Cannabis, as it's ultimate goal is to explore the possibilities presented by Botanical Drug Research. It aims to explore the therapeutic compounds present in other plants such as Hyptis spicigera, Amomum cannicarpum, Angelica sinensis, Salvia potentillifolia and Eucalyptus globulus to name a few. This will be done with the same principles as described above, and aim to develop medicines with clear pharmacological rationales-that will enable physicians to prescribe them.

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