SUMBISSION TO THE PARLIAMENT OF AUSTRALIA CONCERNING

THE REGULATOR OF MEDICINAL CANNABIS BILL 2014

March 13, 2015

Contents

1. Purpose of this Submission

In February of this year, Bedrocan was invited to speak with the office of Sen. Richard Di Natale about our experience producing medicinal-quality cannabis under federal licenses of both the Dutch and Canadian governments. As a result of that meeting, we were asked by Sen. Di Natale's staff to prepare a submission commenting on the proposed Regulator of Medicinal Cannabis Bill (2014) currently under consideration by the Australian Parliament.

This submission offers a contribution to discussions pertaining to the production, distribution, and use of cannabis for medical purposes under a federal authority. We provide context of our experience as a federally licensed controlled substance manufacturer, followed by a summary review of the regulatory environments in which we operate. To the best of our ability, we avoid stating regulatory preferences, preferring instead to suggest possible implications and considerations of the proposed legislation, based on our experience and on the scientific literature.

We will not comment on the merits of medicinal cannabis, leaving to the Australian Members of Parliament to review the available scientific literature on the safety and efficacy of cannabis and its constituents, as well as on illicit use by individuals with serious or chronic conditions in Australia. We trust that the Parliament will make decisions on criminal enforcement and on the production and distribution of what is, as yet, an unapproved drug that will be in the best interest of the health and safety of the Australian people.

Where relevant, this submission is limited to our areas of practical and scientific expertise, which include:

i. Standardized, quality-controlled production of pharmaceutical-grade cannabis under a national health regime
ii. Import and export of cannabis in compliance with the Single Convention on Narcotic Drugs (1961)
iii. The chemistry of cannabis, including chemical analysis methods
iv. Clinical evidence of the use and the efficacy of cannabis for certain indications
v. Diverse models of dispensing cannabis for medical purposes
vi. Epidemiology
vii. Cannabis administration forms
viii. Cannabis in drug development

2. Introduction to Bedrocan

Bedrocan is an international, federally-licensed producer of medicinal-cannabis for patient-use and research. Currently, we produce or dispense quality-controlled cannabis for two nationally authorized medicinal cannabis programs which function in full compliance with international treaty obligations under the Single Convention on Narcotic Drugs (1961).

Since 2003, Bedrocan has been the contracted producer of medicinal cannabis for the Dutch Ministry of Health, Welfare, and Sport. The Ministry's Office of Medicinal Cannabis (OMC) oversees production and distribution of medicinal cannabis as an unapproved drug under Special Access provisions of Dutch and European Union (EMEA) pharmaceutical regulations.

Under these requirements, cannabis for medical use must adhere to the same quality standards that apply to other medicines. Production processes meet Good Agricultural Practice (GAP) and Good Manufacturing Practice (GMP) standards, and are ISO 9000:2008 certified for the production of medicinal cannabis. Each strain is standardized with a defined chemical profile. The composition of Active Pharmaceutical Ingredients (APIs) THC, CBD, and CBN are to within +/-20% of the pre-declared value. In addition, the cannabis is guaranteed free of microbial contaminants (molds, fungi, and bacteria) and heavy metals to levels required of medicines administered into the respiratory tract, as defined in the EMEA Pharmacopeia.

In the Netherlands, medicinal cannabis is available on prescription and dispensed in pharmacies. The Dutch Ministry exports cannabis to Germany, Italy, Finland, and the Czech Republic, where it is also dispensed in pharmacies in accordance with pharmaceutical quality regulations of importing countries, and to Canada, where it is dispensed to patients directly.

Bedrocan's subsidiary, Bedrocan Canada, is licensed by the Canadian Health Ministry (Health Canada) and distributes the same standardized, medicinal-quality cannabis to individuals under the Marihuana for Medical Purposes Regulations (MMPR) as of 2014.

Bedrocan is one of the world's few sources of research-grade cannabis. The OMC exports our research materials to approved researchers around the world. Available materials include: four genetically and chemically standardized strains (two additional strains are near-standardization), placebos to match each strain, cannabis with any desired profile up to 25% THC and 10% CBD, and cannabinoid reference standards up to 98% purity of neutral cannabinoids (delta-9-THC, delta-8-THC, CBN, CBD, CBG, CBC, CBL) and their acidic derivatives (THCA, CBDA, CBGA, CBCA and CBLA). Bedrocan also offers analytical testing of cannabis using validated methods described in a monograph of the Dutch Health Ministry.

We are actively engaged in a number of university and private collaborations for research and commercial purposes. We provide standardized cannabis as a starting raw material for the production of pharmaceutical products, and have published research papers on topics such as administration forms, cannabis chemistry, epidemiology, drug interactions, and more. We are currently engaged in a clinical trial program with a network of pain clinics in the Netherlands with the goal of developing cannabis into a registered medicine.

3. Regulatory Experience

Medicinal Cannabis Regulations in the Netherlands

Regulatory structure

The Dutch Medicinal Cannabis Program was initiated under directive from the Health Ministry in 1999. The Ministry integrated cannabis into the existing framework for medicines, and issued an exemption from the Dutch Opium Act. Under the Opium Act, the use of cannabis for non-medical purposes is prohibited. However, use of small amounts is generally tolerated under a policy of non-enforcement.

In all European countries with existing medicinal cannabis programs (the Netherlands, Finland, Germany, Italy, and the Czech Republic), medicinal cannabis is regulated as an unapproved drug under existing pharmaceutical regulations of the country of use and consistent with regulations of the European Medicines Evaluation Agency (EMEA).

Unapproved drugs have not been determined by regulators to be safe and effective for a target indication. This approval requires a review of data from the completion of three phases of clinical studies of increasing size and narrowing scope toward a target indication. Pharmaceutical regulations in the developed world often allow for the distribution of unapproved drugs under special conditions. These may include: a promising drug intended for an underserved population for which there are few effective alternatives, participation in a clinical trial, use for rare conditions, or others.

As required by the Single Convention, production, domestic distribution, and export of cannabis for medical use in the Netherlands are controlled by the Health Ministry's Office of Medicinal Cannabis (OMC). Import from the Netherlands by importing countries is controlled by various agencies within respective Health Ministries, typically by those responsible for importing medicines.

Under this system, cannabis is integrated into the existing health care system. Quality control is consistent with other medicines, official prescription allows for the same system of professional physician oversight that exists for other medicines, and patients are afforded the same rights and benefits as with the use other medicines, including reimbursement by private health insurers. Cannabis in the Netherlands is now covered by several major private insurance providers; an independent decision of insurers based on reliable quality and anticipated cost savings.

New strains and administration forms are offered after consideration of the scientific basis for the content and form of the proposed product. The Dutch Ministry, in cooperation with Bedrocan and participating pharmacies, are currently developing a method for production of cannabis into an extraction under pharmaceutical conditions to allow for administration via oral ingestion.

Product quality

The OMC contracts a consortium of companies to oversee production: (Bedrocan BV), quality control (Farmalyse BV), and packaging (Fagron BV). The combined process creates an end product that meets GAP and GMP-level standards for the production of herbal medicines.

As an unapproved drug, Bedrocan's cannabis is subject to the same product quality requirements as other medicines. These are:

1) Standardized chemical composition (within +/-20% of the declared value) to ensure consistency and reliability in dosage, and
2) Absence of contaminants to levels appropriate for medicines administered (inhaled) into the respiratory tract, as described in the EMEA Pharmacopeia.[1]

A standardized preparation that is consistently within pre-declared tolerance levels is a requirement of all medicines.[2] This ensures that a known dosage is reliably delivered to patients, and allows patients and health professionals to accurately monitor its effects. Medicines that are inconsistent may interact unpredictably with other drugs, produce unexpected side effects, exacerbate existing health problems (or even cause new ones), or they may not have the intended effect. Even small deviations may influence the medicinal effect.[3]

According to the American Herbal Products Association, standardization is the complete body of information and controls that serves to optimize the batch-to-batch consistency of a botanical product. It is achieved by reducing the inherent variation of natural product composition through quality assurance practices applied to agricultural and manufacturing processes.[4] This standard is also applied to herbal medicines by the World Health Organization and has been adopted internationally.[5]

For cannabis, this is particularly important as there is considerable variability in chemical composition, both in levels of active ingredients[6] and in administration forms.[7] Plants can contain many active compounds, each with their own unique biological effect. These compounds may interact with each other to produce a final effect which may vary according to their concentrations.[8] Research suggests this may be true in cannabis. THC in isolation may produce a different effect compared with THC delivered in herbal cannabis.[9] This may be due to a number of other compounds which have been shown to be biologically active.[10]

Because the most common method of administration of cannabis is inhalation, the OMC requires that levels of contaminants be at levels required of medicines that are administered into the respiratory tract (inhalation). This is important for individuals who may have compromised immune systems, such as in HIV/AIDS or cancer, as a lung infection caused by contaminated cannabis may have particularly serious implications. See Appendix for a list of studies on possible health problems of using contaminated cannabis.

The OMC currently offers 5 genetically and chemically distinct cannabis strains in Dutch pharmacies (more are offered for export). Each strain has a standardized composition of the cannabinoids THC, CBD, and CBN. New strains are released on a case-by-case basis if there is determined to be a justification in the scientific literature. Strains are selected for their chemical profile and are mostly developed from popular recreational varieties to increase patient adherence to the medical product as a desirable alternative to the illicit market.

Currently cannabis extracts of medicinal quality are not available in pharmacies in the Netherlands. However, Bedrocan is currently working with the OMC and pharmacy partners on the production of cannabis extracts under pharmaceutical conditions in order to offer this as a viable alternative administration form.

Distribution

In the Netherlands, medicinal cannabis is dispensed by the Office of Medicinal Cannabis under existing regulations for medicines.

Bedrocan cannabis is packaged into 250 gram containers, where the OMC collects it and outsources to a contracted company for the required quality control (gamma irradiation and testing). After this, it is packaged for the end-user in 5 gram containers by a pharmaceutical packaging company also contracted by the OMC. The OMC then sends the 5-gram containers to pharmacies as needed to fill patient orders.

The cannabis is dispensed in pharmacies alongside other drugs. In this way, professional pharmacists provide the standard, professional level of health care to patients, as with other medicines. The pharmacist is able to complement the role of the physician in monitoring drug interactions, contra-indications, side effects, or adverse events. They are also able to provide the patient with a professional standard of accurate, science-based information on the use cannabis for medical purposes.

On the official prescription, the physician indicates the strain with the desired chemical profile to be used, as well as the daily amount. There are no limits on prescription or possession amounts, as this is left to physicians' discretion, as with other medicines, and suspected diversion is monitored cooperatively by both the physician and the pharmacist, also as with other medicines.

The OMC provides a list of indications for which there is evidence cannabis may be efficacious. However, cannabis may be prescribed "off-label" for any indication, as determined by the prescribing physician.

As mentioned above, today, medicinal cannabis is reimbursed by several major health insurance providers in the Netherlands.

Similar regulations for pharmacy distribution apply in other European countries. As there is no established dosage for herbal cannabis, in some countries (i.e. Italy) cannabis is exported by the Dutch Ministry in bulk packages, which are then prepared by compounding pharmacists in the importing country.

Of particular note is the relative number of people accessing cannabis for medical purposes in the Netherlands, compared with program sizes of other countries. Data indicate between 5-8 individuals per 100,000 use cannabis for medical purposes in the Netherlands.[11] This is notably lower than in Canada (est. 35 per 100,000) and in the published literature.[12] [13] There is some indication of correlation between recreational use rates and medicinal use rates. Rates of recreational use of cannabis in the Netherlands are lower than in Canada. However, there is a significant difference in medicinal use rates of cannabis, even considering this factor. Possible conflating factors include the longstanding "coffee shop" environment in the Netherlands, which may be an established choice for patients due to available selection, convenience, or stigma associated with discussing cannabis use with their doctor. Still, the program in the Netherlands continues to undergo significant growth and rate of growth in the recent years.

Communication and marketing

As an unapproved narcotic drug, the marketing of cannabis is prohibited by pharmaceutical regulations. As the administrator of the medicinal cannabis program, the Dutch OMC acts as a

source of science-based information for physicians and patients. For doctors, this is presented in a form similar to other pharmaceutical preparations. This information is available on the OMC website, and includes information on contra-indications, side-effects, known drug interactions, possible indications for which the use of cannabis may have an effect, and the standardized chemical profiles of available strains.

Bedrocan is prohibited from marketing to patients and directly to physicians. However, some pharmaceutical distributors and importers do market directly to physicians in other countries, such as Italy. In addition, we do engage in some activities that are allowed. We sponsor independent professional continuing medical education (CME) courses intended to educate physicians on the current state of research on cannabinoid drugs, which includes approved drugs as well as cannabis. We also sponsor cannabinoid research organizations, and publish and disseminate research on a variety of topics. We also engage in media activities about our work, and hold an annual educational "Masterclass" intended to instruct diverse professionals, including government regulators, scientists, health care professionals, and patient advocates from around the world in a 1-week intensive instruction on the science and regulation of cannabis for medical use. This takes place each Autumn, in the Netherlands.

Medicinal Cannabis Regulation in Canada

Bedrocan licenses a Canadian company, Bedrocan Canada (Bedrocan Cannabis Corp.), which is authorized by the Canadian Ministry of Health (Health Canada) to produce cannabis for medical use by authorized individuals in Canada.

Regulatory Structure

In contrast to Europe, in Canada cannabis is not regulated under existing health care regulations for pharmaceutical drugs, but by its own, separate regulatory structure.

Since the late 1990's, Canadians with certain pre-defined medical conditions could apply to the federal government to obtain legal authorization to possess and cultivate cannabis for medical purposes. The Marihuana Medical Access Regulations (MMAR) was initiated by a court ruling which affirmed the right of Canadians to access cannabis for medical purposes to be a fundamental right under Section 7 of the *Canadian Charter of Rights and Freedoms* of the Canadian Constitution.[14] Since the 1990s, the initially restrictive program continued to expand through court challenges. The courts ruled that without an effective medical program, the government would lose the constitutional authority to retain the criminal prohibition on cannabis, that is, the criminal law would cease to apply to all users, medical or recreational. [15]

Initially, Health Canada regulated cannabis as an unapproved drug under exemptions allowed by existing pharmaceutical regulations (a Section 56 exemption). However, this system was deemed inaccessible, and was successfully challenged in court. Canadian courts have ruled on: inaccessibility of physicians willing to sign authorizations, the quality of cannabis, the list of qualifying medical conditions, inaccessibility of "designated growers", and obstructions due to the bureaucracy of the program. Rulings have mandated program expansion. [16] The most recent expansion was the creation of the Marihuana for Medical Purposes Regulations (MMPR) of 2014, which allows for the licensing and distribution of cannabis directly to authorized users by commercial producers.

Initially, the program allowed participants to receive cannabis from Health Canada, from a designated provider, or by growing their own. However, as the MMAP had been the subject of

criticisms of inaccessibility, a side industry developed to meet a larger market demand that appeared not to be met by the official program. This industry consisted of Compassion Clubs, storefronts, delivery services, and individuals who provided cannabis to patients outside of the official program. However, this quasi-legal industry was the center of criticism itself, as some suggested that abuse and diversion may have been widespread.

The success and constitutionality of the current MMPR depend upon access to both the program and to cannabis in a form patients require. Lawsuits continue to challenge both, as some professional health care organizations oppose their participation in the parallel system, cannabis is not distributed in pharmacies, is rarely reimbursed by insurance, and alternate administration forms are not allowed, even when produced by patients themselves for personal use. Some of these problems may stem from the parallel system that is not fully integrated into the existing structure for the regulation of medicines.

Product Quality

In contrast to European countries, Health Canada's product quality requirements are different from those required of other medicines. Health Canada does not require cannabis sold to patients to be standardized with a consistent chemical composition. Instead, requirements are limited to accurate product labelling for THC and CBD. In addition, Health Canada does not require cannabis to meet contaminant levels for administration into the respiratory tract (inhalation). Instead, cannabis is required to meet contaminant levels for herbal medicinal products.

Initially, Health Canada required cannabis produced by the contracted government producer to be both standardized and to adhere to contaminant standards for inhalation (quality standards never applied to individuals authorized to grow for personal use, which became relevant when these individuals began producing for larger numbers of people). However, these quality requirements were removed under the MMPR in 2014. This may have been because, in stakeholder consultations, there was vocal criticism from patients of the perceived quality of the government produced cannabis.[17] Since MMPR initiation, there have been product recalls due to high levels of contamination, even with the reduced standards, as well as recalls due to inaccurate labelling of product chemistry.

Under the MMPR, licensed producers are allowed to bring any strains to the market, without prior approval. Product labels must include levels of THC and CBD only. Currently there are dozens of cannabis strains available for patient use.

Cannabis extracts and other concentrated forms are prohibited in Canada, although this is being challenged in Canadian courts.

Distribution

In contrast to Europe, cannabis is dispensed to individuals in Canada not on prescription, but on an "authorization" to possess cannabis. This authorization does not specify the particular cannabis product or chemical profile, as this would be of limited value due to the lack of standardized products available. Instead, the authorization allows patients to source their choice of cannabis from the wide variety of products available from approximately 2 dozen producers.

While in the past, authorization to possess cannabis was limited to individuals who met a list of qualifying conditions, this restriction has been removed as of 2014 under the MMPR. Individuals

may now be authorized for any condition, left to the discretion of the physician (and in some provinces, a Nurse Practitioner). Authorizations last for one year.

There has been some criticism of wide authorization practices of some physicians. This criticism has been balanced by the practical experience of physicians in dealing with patients who use cannabis, and as patients have reported difficult finding a physician willing to provide the authorization. Criticism has focused on physicians charging an additional fee for cannabis authorization, and a possible reduction of the standard of care in some practices where large numbers of patients are authorized, and may not be seen or monitored again by the physician until the next authorization, one year later.

There are no standard package amounts, although authorized individuals are prohibited from possessing an amount greater than a 30 day supply, according to the daily amount authorized by the physician, or 150 grams, whichever is the lesser amount.

Labelling is required to show an accurate chemical profile of the batch, and to display an “N” to indicate cannabis is a narcotic drug.

Cannabis is not dispensed in pharmacies, but rather directly to patients from the producer. This is done over the phone or internet, as no face-to-face sales are allowed under the MMPR. In addition, while in Europe cannabis is dispensed by licensed pharmacists, no professional qualifications are required to dispense cannabis in Canada, and the quality or accuracy of information presented to patients may not be closely monitored.

Because cannabis for medical use is regulated by a parallel system, and not under existing regulations for medicines, there has been some difficulty in integration with the existing healthcare system. For example, there was vocal opposition of participation in the program from professional pharmacist and physician organizations. In addition, cannabis is not available in pharmacies and generally not reimbursed by health insurance in Canada.

Communication and marketing

In Canada, cannabis is classified as a narcotic drug. Therefore, marketing to patients is prohibited by Canadian regulations. Communication on products is limited to the name of the company and product as well as the chemical profile. However, marketing to physicians is not prohibited, and is a common activity of licensed cannabis producers.

The early stages of the MMPR have led to some uncertainty in what marketing practices are allowed. Health Canada recently issued warning letters on marketing activities to nearly all Canadian producers, including Bedrocan’s licensee. This uncertainty may be due to a number of factors. As cannabis is not covered under existing pharmaceutical regulations, organizations which typically assist the pharmaceutical industry in development of materials for Health Canada approval did not accept submissions from cannabis producers.

In 2014, Health Canada acted in its capacity as a resource for health professionals to access the latest science-based information on cannabis by compiling one of the most comprehensive reviews of the science of cannabis to date. This is available on the Health Canada website.

4. Substantive Comments:

1. Part I, Section 4: Simplified outline of this Act: "Products included in the register are regulated under this Act, rather than under the Therapeutic Goods Act 1989 ."

This outlines the basis for regulatory differences between the European and Canadian medicinal cannabis programs. The Dutch model utilizes existing pharmaceutical regulations to provide a framework for medicinal cannabis production and distribution. The Canadian model offers a parallel structure which overlaps with the existing healthcare system at certain points, such as marketing restrictions and the role of physicians as gatekeepers for authorization. Parliament should consider whether the proposed parallel system may make integration with other aspects of health care, such as reimbursement, professional dispensing of medicines, or physician participation more challenging.

2. Part I, Section 5: Definitions:

"Cannabis product means:

(a) cannabis, or a product derived from cannabis, that is intended for medicinal use; or
(b) a synthetic version, that is intended for medical use, of a product derived from cannabis"

This definition allows for the manufacture and sale of natural and synthetic preparations of chemical compounds for medical purposes outside of existing pharmaceutical regulations.

Cannabinoid products include approved cannabinoid drugs, such as Marinol, Cesamet, and Sativex. This language may allow these drugs to be regulated outside of the functioning medical system. In addition, it may allow for the manufacture and sale for medical purposes of concentrated forms of over 80 additional synthetic or natural cannabinoids.[18] Many of these natural (or *phyto*) cannabinoids have rarely, if ever, been studied in humans.[19] The majority of these, when present, are found in negligible amounts. Different cannabinoids are known to have demonstrably different activity, and it is unclear what the effects of highly concentrated levels of synthetic or natural versions of many of these minor cannabinoids may be.

In addition, it is unclear whether the term "version" refers to a synthetic preparation that is chemically identical to a product derived from cannabis, or one that is chemical similar. If chemical similarity is sufficient, this opens the possibility of the sale of an even greater number of chemicals with uncertain safety and efficacy under an assertion of medical use.

Given the wide availability and popular use of cannabis, providing a quality-controlled source to be used by patients under physician supervision may reduce legal and health harms that may be associated with use. In addition, there is significant interest in determining, through clinical research, any positive health benefits particular cannabis strains may have for varying conditions. Independent clinical research is moving forward in this area. However, Parliament should take care when creating a commercial incentive to market a wide class of synthetic or natural drugs for

medical purposes without a requirement or incentive to demonstrate safety and efficacy, as required under regulations for existing medicines.

3. Part II, Division 2, Section 15: Cannabis products:

i. "Cannabis products are to be taken to be separate and distinct from other cannabis products if they have:
    1. (a) a different formulation, composition, or design specification, or
    2. (b) a different strength or size, or
    3. (c) a different dosage form or model, or
    4. (d) a different name, or
    5. (e) different indications, or
    6. (f) different directions for use, or
    7. (g) a different type of container (disregarding container size)."

In order to enforce provisions (a), (b), and (e), pre-determined specification values must be declared for each cannabis product, along with tolerance levels for each class of product (such as herbal strains, extractions, etc.).

Chemical variability is common in plants, and there is considerable variability in cannabis.[20] In order for cannabis products to be separate and distinct, a pre-declared, standardized chemical composition is required for each product.

For a description of standardization in botanical medicines, see the description of product quality under the Dutch program in the sections above.

In addition, it is not clear what evidence may be required to differentiate cannabis products according to a particular indication under *e) Different indications*.

Under the Therapeutic Goods Act, establishing a target indication for a medicine takes place in drug development via a rigorous scientific process. However, cannabis products are not regulated by the Therapeutic Goods Act, therefore it is not clear what scientific evidence may be required to market specific cannabis products as effective for different indications.

Claims are often made connecting certain cannabis strains with specific indications. While anecdotal reports of patients are useful and necessary, these claims are often not supported by scientific evidence. Such claims become particularly problematic in referring to cannabis that is non-standardized, as a claim of efficacy may be made for products that are marketed under the same name, but which may vary significantly in their chemical composition batch-to batch.

The marketing of different strains of cannabis for specific indications, without proper evidence to support those claims, may create confusion among patients and doctors. Care should be taken that the evidence required to make claims of efficacy of a medical product for a certain indication should remain at a high level of quality.

4. Part II, Division 3, Section 16 - Medicinal Cannabis Licensing Scheme, Subsection 1(e) providing regulated medicinal cannabis products to authorised patients and authorised carers;

In considering proposed mechanisms of distribution, qualifications of those distributing should be considered. Active compounds in cannabis may interact with other drugs, cause adverse events, and may be harmful in some at-risk individuals.[21] Individuals authorized to dispense cannabis to patients and carers should hold the proper professional qualifications required for the distribution of other medicines. This may include licensed pharmacists, and/or pharmacy technicians under the supervision of licensed pharmacists.

In addition, these professionals should receive proper education on the scientific evidence of cannabis, including on practical matters, such as administering or dosing cannabis.

5. Marketing cannabis

As the Therapeutic Goods Act does not apply to cannabis products, it is unclear what regulations will control marketing of cannabis for medical purposes. Parliament should consider whether restrictions should be similar to the marketing of other drugs for medical use. In addition, they should consider the status of cannabis as an unapproved drug and as a narcotic controlled substance.

At the same time, regulations should also recognize that research on cannabis and cannabinoids is widely available, and that the public has an interest in this research, as long as it is presented in proper context. In the communication of scientific information, appropriate context should be given regarding the strength of particular studies, as well as to the significance of their findings compared with the larger body of research on a particular topic.

In addition, opportunities should be defined for the education of health professionals on the science of cannabis and cannabinoids, through professional continuing education courses or dissemination of information of similar professional quality.

6. Part II, Division 6 - Medicinal Cannabis Standards, Section 23, Subsection 2(a)

In determining standards for cannabis products, standards should also be considered for testing cannabis. Varying laboratory methods may contribute to inconsistent analytical results.[22]

5. Appendix

Studies on Harms Associated with Contaminated Cannabis

1. "Examination of fungal growth and aflatoxin production on marihuana". *Llewellyn GC, O'Rear CE. Mycopathologia. 1977 Dec 16;62(2):109-12.*

2. "Allergic bronchopulmonary aspergillosis associated with smoking moldy marihuana". *Llamas R, Hart DR, Schneider NS. Chest. 1978;73:871–2.*

3. "Marijuana smoking and fungal sensitization". *Kagen SL, Kurup VP, Sohnle PG, Fink JN. J Allergy Clin Immunol. 1983;71:389–93.*

4. "Allergenic fungi and actinomycetes in smoking materials and their health implications". *Kurup VP, Resnick A, Kagen SL, Cohen SH, Fink JN. Mycopathologia. 1983 Apr 22;82(1):61-4.*

5. "Possible risk of invasive aspergillosis with marijuana use during chemotherapy for small cell lung cancer". *Sutton S, Lum BL, Torti FM. Drug Intell Clinical Pharm 1986; 20: 289-91.*

6. "Fatal aspergillosis associated with smoking contaminated marijuana, in a marrow transplant recipient". *Hamadeh R, Ardehali A, Locksley RM, York MK. Chest. 1988 Aug;94(2):432-3.*

7. "Pulmonary aspergillosis in the acquired immunodeficiency syndrome". Denning DW, Follansbee SE, Scolaro M, Norris S, Edelstein H, Stevens DA. N Engl J Med. 1991 Mar 7;324(10):654-62.

8. "Successfully treated invasive aspergillosis associated with smoking marijuana in a renal transplant recipient". *Marks WH, Florence L, Leiberman J, Chapman P, Howard D, Roberts P et al. Transplantation 1996; 61: 1771-4.*

9. "Invasive aspergillosis in liver transplant recipients in the 1990s." *Singh N, Arnow PM, Bonham A, Dominguez E, Paterson DL, Pankey GA, Wagener MM, Yu VL. Transplantation. 1997 Sep 15;64(5):716-20.*

10. "Risk factors and outcomes associated with identification of Aspergillus in respiratory specimens from persons with HIV disease. Pulmonary Complications of HIV Infection Study Group". *Wallace JM, Lim R, Browdy BL, Hopewell PC, Glassroth J, Rosen MJ, Reichman LB, Kvale PA. Chest. 1998 Jul;114(1):131-7.* [Cannabis not associated with Aspergillus]

11. "Sino-orbital aspergillosis in acquired immunodeficiency syndrome." *Johnson TE, Casiano RR, Kronish JW, Tse DT, Meldrum M, Chang W. Arch Ophthalmol. 1999 Jan;117(1):57-64.*

12. "Fungal contamination of tobacco and marijuana". *Verweij PE, Kerremans JJ, Voss A, Meis JF.JAMA. 2000;284:2875.*

13. "Early invasive pulmonary aspergillosis in a leukemia patient linked to aspergillus contaminated marijuana smoking". *Szyper-Kravitz M, Lang R, Manor Y, Lahav M. Leuk Lymphoma. 2001 Nov-Dec;42(6):1433-7.*

14. "Aggrevation of allergic bronchopulmonary aspergillosisby smoking marijuana". *Kouevidjin G, Mazieres J, Fayas S, Didier A. Revue Francias d'Allergologie et d'Immunologie Clinique. 2003;43:192–4.*

15. "Invasive pulmonary aspergillosis associated with marijuana use in a man with colorectal cancer". *Cescon DW, Page AV, Richardson S, Moore MJ, Boerner S, Gold WL. J Clin Oncol. 2008 May 1;26(13):2214-5. doi: 10.1200/JCO.2007.15.2777.*

16. "Chronic necrotising pulmonary Aspergillosis in a marijuana addict: a new cause of amyloidosis". *Bal A, Agarwal AN, Das A, Vikas Suri, Varma SC. Pathology. 2010;42:197–200.*

17. "Talcum induced pneumoconiosis following inhalation of adulterated marijuana, a case report*". Andreas Hans Scheel, Daniel Krause, Helmut Haars, Inge Schmitz, and Klaus Junker. Diagn Pathol. 2012; 7: 26. Published online 2012 March 15.*

18. *"The large spectrum of pulmonary complications following illicit drug use: Features and mechanisms," Bruno Mégarbanea, Lucie Chevillard, Chemico-Biological Interactions, Oct. 2013.*

19. *"Determination of Pesticide Residues in Cannabis Smoke". Nicholas Sullivan, Sytze Elzinga, and Jeffrey C. Raber, Journal of Toxicology, April 2013.*

List of Bedrocan Publications

(Some publications listed under multiple headings)

Administration Forms

Cannabinoids act differently when they are administered into the body in different ways, such as ingesting or inhaling. We work to understand these differences. In addition to the studies below, our team also conducted the research which allowed the Medic® Vaporizer (storz-bickel.com) to become an approved medical device in Canada, which it has been since 2008.

1. Hazekamp. *Evaluation of a Vaporizing Device (Volcano) for the Pulmonary Administration of Tetrahydrocannabinol*. J. Pharm. Sci. **2006**; 95(6): 1308-1317.
2. Hazekamp. *Cannabis tea revisited: A systematic evaluation of the cannabinoid composition of cannabis tea*. Journal of Ethnopharmacology **2007**; 113, 85–90.
3. Zuurman, Hazekamp. *Effect of intrapulmonary tetrahydrocannabinol administration in humans. J Psychopharmacol.* **2008**; 22(7): 707-716.
4. Romano, L. and Hazekamp, A. *Cannabis Oil: chemical evaluation of an upcoming cannabis-based medicine*. Cannabinoids **2013**; 1(1): 1-11.
5. Hazekamp, Ware, Muller-Vahl, Abrams, Grotenhermen. *The medicinal use of cannabis and cannabinoids–an international cross-sectional survey on administration forms*. J Psychoactive Drugs **2013**; 45(3): 199-210.
6. Nadia Solowij, Samantha J Broyd, Hendrika H van Hell and Arno Hazekamp. *A protocol for the delivery of cannabidiol (CBD) and combined CBD and Δ9-tetrahydrocannabinol (THC) by vaporisation*. BMC Pharmacology and Toxicology **2014**, 15:58.

Social Research

Cannabis is used by many thousands of people to treat symptoms of a health condition, often outside the care of a physician. In our effort to bridge the gap between the laboratory and the realities of patient use, we conduct behavioral studies to collect data on dosing, indications, administration forms, cannabis varieties, and more.

1. Hazekamp. *An evaluation of the quality of medicinal grade cannabis in the Netherlands.* Cannabinoids. **2006**; 1(1):1-9.
2. Gieringer, Hazekamp. *How accurate is potency testing?* O'Shaughnessy's. Autumn **2011**: 17.

3. Hazekamp, Ware, Muller-Vahl, Abrams, Grotenhermen. *The medicinal use of cannabis and cannabinoids–an international cross-sectional survey on administration forms. J Psychoactive Drugs* 2013; 45(3): 199-210.
4. Hazekamp, Heerdink. *The prevalence and incidence of medicinal cannabis on prescription in The Netherlands.* Eur J Clin Pharmacol. 2013; 69(8):1575-80.

Cannabis Chemistry and Variety Research

We support academic research on our cannabis varieties and also conduct our own. Because our strains are research-grade and fully standardized, results can be compared across many studies that use the same varieties. Some published studies on our own varieties include:

1. Hazekamp et al. *Preparative isolation of cannabinoids from Cannabis sativa by centrifugal partition chromatography*. Journal of Liquid Chromatography & Related Technologies 2004; 27(15): 2421-2439.
2. Hazekamp. *Quantitative Analysis of Cannabinoids from Cannabis sativa Using 1H-NMR*. Chem. Pharm. Bull. 2004; 52(6): 718-721.
3. Hazekamp. *Chromatographic and spectroscopic data of cannabinoids from Cannabis sativa L*. Journal of Liquid Chromatography & Related Technologies 2005; 28: 2361-2382.
4. Hazekamp. *Structure elucidation of the tetrahydrocannabinol complex with randomly methylated beta-cyclodextrin*. Eur. J. Pharm. Sci. 2006; 29: 340-347.
5. Bastola, Hazekamp. *Synthesis and spectroscopic characterization of cannabinolic acid*. Planta Medica 2007; 73: 1-3.
6. Fischedick, Hazekamp. *A Qualitative and Quantitative HPTLC Densitometry Method for the Analysis of Cannabinoids in Cannabis sativa L*. Phytochem. Anal. 2009; 20: 421–426.
7. Fischedick, Hazekamp. *Metabolic fingerprinting of Cannabis sativa L., Cannabinoids and Terpenoids for Chemotaxonomic and Drug Standardization Purposes*. Phytochemistry 2010; 71(17-18): 2058-2073.
8. Fischedick. *Cannabinoid Receptor 1 Binding Activity and Quantitative Analysis of Cannabis sativa L. Smoke and Vapor*. Chem. Pharm. Bull. 2010; 58(2): 201-207.
9. Hazekamp, Fischedick. *Cannabis – From Cultivar to Chemovar*. Drug Testing and Analysis 2012; 4: 660-667.
10. Erkelens, Hazekamp. *That which we call Indica, by any other name would smell as sweet. An essay on the history of the term Indica and the taxonomical conflict between the monotypic and polytypic views of Cannabis*. Cannabinoids 2014; 9(1): 9-15.

Administration Forms and Pharmacodynamics

1. Hazekamp. *Evaluation of a Vaporizing Device (Volcano1) for the Pulmonary Administration of Tetrahydrocannabinol*. J. Pharm. Sci. **2006**; 95(6): 1308-1317.
2. Pomahacova. *Cannabis smoke condensate III: The cannabinoid content of vaporised Cannabis sativa.* Inhalation Toxicology **2007**; 21(13): 1108–1112.
3. Hazekamp. *Cannabis tea revisited: A systematic evaluation of the cannabinoid composition of cannabis tea*. Journal of Ethnopharmacology **2007**; 113: 85–90.
4. Fischedick. *Cannabinoid Receptor 1 Binding Activity and Quantitative Analysis of Cannabis sativa L. Smoke and Vapor*. Chem. Pharm. Bull. **2010**; 58(2): 201-207.
5. Brenneisen. *Plasma and urine profiles of Δ9-tetrahydrocannabinol and its metabolites 11-hydroxy-Δ9-tetrahydrocannabinol and 11-nor-9-carboxy-Δ9-tetrahydrocannabinol after cannabis smoking by male volunteers to estimate recent consumption by athletes*. Analytical and Bioanalytical Chemistry **2010**; 396(7): 2493-2502.
6. Kowal, Hazekamp. *Modulation of cognitive and emotional processing by cannabidiol: the role of the anterior cingulate cortex*. Front. Hum. Neurosci. **2013**; 7: 147.
7. Kowal, Hazekamp et al. *Cannabis and creativity: highly potent cannabis impairs divergent thinking in regular cannabis users*. Psychopharmacology (Berl) **2014**; in press

Review papers and book chapters

1. Hazekamp, Grotenhermen. *Review on clinical studies with cannabis and cannabinoids 2005-2009*. Cannabinoids **2010**; 5: 1-21.
2. Hazekamp et al. *Chemistry of cannabis*. In: Comprehensive Natural Products II Chemistry and Biology; Mander L, Lui HW, Eds. Elsevier, Oxford **2010**; volume 3: 1033–1084.
3. Hazekamp, Pappas. *Self-Medication with Cannabis*. In: Handbook of cannabis. Pertwee R, Ed. Oxford University Press, Oxford **2014**; chapter 17.

6. References

[1] Council of Europe – European Directorate for the Quality of Medicines. *European Pharmacopoeia. 5th Edition – Supplement 5.6*. Strasbourg: Council of Europe; 2006.

[2] International Conference on Harmonization. *Harmonised Tripartite Guideline: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*. Geneva; 2000.

[3] Scholten, Willem, *The New EU GACP Rules: Are Good Practices Enough if they Do Not Result in Batch-to-Batch Consistency?* Drug Inf J. 2003.

[4] American Herbal Products Association. *White Paper on Standardization*. 2003.

[5] World Health Organization, *Guidelines on Good Manufacturing Practices for Herbal Medicines*. WHO Press. Geneva. 2007.

[6] Romero, Dennis. *Marijuana Strains Like OG Kush are Meaningless, Expert Says*. LA Weekly. Dec. 3, 2013.

[7] Hazekamp, Ware, Muller-Vahl, Abrams, Grotenhermen. *The medicinal use of cannabis and cannabinoids–an international cross-sectional survey on administration forms. J Psychoactive Drugs* **2013**; 45(3): 199-210.

[8] American Herbal Products Association. *White Paper on Standardization*. 2003..

[9] Hazekamp, A., Ware, M., et al., "*The Medicinal Use of Cannabis and Cannabinoids—An International Cross-Sectional Survey on Administration Forms*," Journal of Psychoactive Drugs, 45 (3), 199–210, 2013.

[10] Russo, Ethan, "*Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects*," British Journal of Pharmacology, 2011.

[11] S Hazekamp, Heerdink. The prevalence and incidence of medicinal cannabis on prescription in The Netherlands. Eur J Clin Pharmacol. 2013; 69(8):1575-80.

[12] Hazekamp, A. and Pappas, G. Self-medication with cannabis. The Cannabis Handbook, Oxford University Press, Ch. 17; 2014.

[13] Ogborne, A.C., Smart, R.G., Weber, T. and Birchmore-Timney, C. (2000). Who is using cannabis as a medicine and why: an exploratory study. Journal of Psychoactive Drugs, 32, 435-443..

[14] R. v. Parker, 2000 CanLII 5762 (ON CA)

[15] Belle-Isle, Lynne, *'Cannabis as Therapy for People Living with HIV/AIDS. "Our Right, Our Choice"'*, Canadian AIDS Society. 2006.

[16] Belle-Isle, Lynne, *'Cannabis as Therapy for People Living with HIV/AIDS. "Our Right, Our Choice"'*, Canadian AIDS Society. 2006

[17] Health Canada. Stakeholder Consultations. Document Released under Access to Information Act. 2012.

[18] Hazekamp, Arno. Medicinal Use of Cannabis: A review. Department of Plant Metabolomics. Leiden University Leiden, The Netherlands. 2009.

[19] Russo, E.B. (2011). Taming THC: Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. British Journal of Pharmacology, 163, 1344-1364.

[20] Romero, Dennis. *Marijuana Strains Like OG Kush are Meaningless, Expert Says*. LA Weekly. Dec. 3, 2013

[21] Curran, H. Valarie and Morgan, Celia J.A. "Desired and Undesired Effects of Cannabis on the Human Mind and Psychological Well-Being," The Cannabis Handbook, Oxford University Press, Chapter 36, pp. 647-660; 2014.

[22] Gieringer, D., and Hazekamp, A. How Accurate is Potency Testing? O'Shaughnessy's. Autumn, 2011.