No. T-2030-13

FEDERAL COURT

BETWEEN:

NEIL ALLARD
TANYA BEAMISH
DAVID HEBERT
SHAWN DAVEY

PLAINTIFFS

AND:

HER MAJESTY THE QUEEN
IN RIGHT OF CANADA

DEFENDANT

AFFIDAVIT OF TODD CAIN

I, **Todd Cain**, of the City of Ottawa, in the Province of Ontario, SOLEMLY AFFIRM AND DECLARE:

1. I am an employee of Health Canada, currently working as Executive Director Market Development for the Healthy Environments and Consumer Safety Branch (HECSB). I report directly to Hilary Geller, Assistant Deputy Minister, and Health Canada.

2. I hold a Bachelor in Public Administration degree from Carleton University and a Master of Industrial and Labour Relations degree from Cornell University. I have extensive private and public sector experience in the areas of management, organizational change,

strategic business initiatives and change management. My Curriculum Vitae is attached at **Exhibit "A"**.

3. My current responsibilities include supporting the transition from the *Marihuana Medical Access Regulations* (MMAR) to the *Marihuana for Medical Purposes Regulations* (MMPR) by identifying and resolving issues in the development and establishment of a stable supply base for medical marihuana.

4. My role includes determining the financial incentives behind participating in licenced production, identifying likely sectors of industry that may be interested in participating, identifying and reaching out to research applicants based on their participation in other HC programs.

5. As such, I have personal knowledge of the evidence sworn to in this affidavit, save and except where any of the following information is stated to be based on information and belief, in which case I state the source of the information and believe that information to be true.

The Transition to the New Model: Marihuana for Medical Purposes Regulations

6. Since June 2013, the MMPR and the MMAR have operated concurrently. The MMAR will be repealed on March 31, 2014. As of April 1, 2014, the MMPR will provide the legal means for Canadians who have the support of a medical practitioner to obtain access to dried marihuana for medical purposes. Under the MMPR, individuals who intend to use dried marihuana for medical purposes are required to register with a Licensed Producer by presenting a signed medical document which authorizes them to use dried marihuana for medical purposes. Personal and designated production will no longer be an option for obtaining dried marihuana for medical purposes.

7. The MMPR are intended to improve significantly the way in which individuals access marihuana for medical purposes, while at the same time, to reduce risks to individual and public health, security and safety. The MMPR provide for expanded options regarding who may sign a medical document, taking into account provincial law and professional bodies, and they impose no limit on the strain of dried marihuana Licensed Producers may offer for sale.

8. In fact, the MMPR provide that, with specific authorizations from Health Canada, Licensed Producers may purchase marihuana seeds or marihuana plants from individuals who hold valid Personal Use Production Licenses or Designated Person Production Licenses until the repeal of the MMAR, making it possible for a Licensed Producer to

cultivate and sell an individual's preferred strain of marihuana. I am advised by Jacinthe David, Manager, Licensing and Permits Division, Office of Controlled Substances, and believe that the majority of new Licensed Producers have availed themselves of this option.

9. The MMPR require that the dried marihuana Licensed Producers offer for sale is produced in compliance with good production practices, and that in carrying out their business, Licensed Producers meet security requirements set out in the regulations and keep records in accordance with the regulations. These requirements are similar to those imposed on other drugs for therapeutic purposes. The *Food and Drugs Act* applies to Licensed Producers, as it does with other narcotics for medical use. Licensed Producers must not operate in a dwelling house. Health Canada will inspect Licensed Producers for compliance purposes.

10. Under the MMPR, individuals who use dried marihuana for medical purposes will no longer require Health Canada approval.

11. To facilitate the transition from the MMAR to the MMPR and, in particular, to the use of Licensed Producers, Health Canada created a Market Development Team ("the Team"), reporting directly to the Assistant Deputy Minister and operating independently from the Licensing and Permits team. This team was created to work with departmental officials responsible for transition from the MMAR and implementation of the MMPR, as well as with external entities and potential Licensed Producer applicants.

12. It was also part of the team's responsibility to design and implement a strategy to facilitate the transition from personal to Licensed Producer production of dried marihuana for medical purposes. Specifically, we, the team, engaged with potential applicants for production licenses, and others, to encourage understanding of the potential marketplace and to facilitate the application process.

13. I was personally charged with the responsibility for development and implementation of a comprehensive strategy to:

    a. Create a timeline for managing the transition from personal to Licensed Producer production of dried marihuana for medical purposes;

    b. Develop models to estimate demand and supply and create strategies for securing sufficient dried marihuana for medical purposes to meet demand during the transition from the MMAR to the MMPR, including the period of time after

October 1, 2013, when no new or amended production licenses would be issued, and the time frame following MMAR repeal on March 31, 2014;

c. Generate and implement a plan to encourage and to promote applications from potential Licensed Producers with the goal of ensuring that during transition to, and early days of the new industry, conditions were in place to create reasonable legal access to a quality supply of dried marihuana for medical purposes;

d. Work with the Licensing and Permits team to streamline the application process to make it accessible to potential applicants for production licenses (see the complete application package, including the Guidance Document, available on the Health Canada Website at http://www.hc-sc.gc.ca/dhp-mps/marihuana/info/app-demande-eng.php and attached as **Exhibit "B"**); and

e. Devise contingency plans for accessing a supply of dried marihuana to meet demand, in the event that:

i. insufficient applications for production licences were received;

ii. an inadequate number of applicants applied or failed to meet security and other regulatory requirements; or

iii. the application process did not unfold in sufficient time to allow newly Licensed Producers to cultivate, grow, harvest, and make dried marihuana available in sufficient quantities to meet demand.

Ongoing Reasonable Access to Quality Dried Marihuana for Medical Purposes

14. The coming into force of the MMPR establishes a new production and delivery system for medical marihuana in Canada. It was and remains a Health Canada priority that a continuous, stable and adequate supply of dried marihuana for medical purposes is available during the transition period and beyond.

15. Given the timelines associated with the transition from the MMAR to the MMPR, Health Canada initiated several strategies to provide for an adequate and timely supply of dried marihuana for medical purposes under the MMPR.

16. One of the primary strategies has been to conduct an information campaign to encourage applications for production licenses under the MMPR. The goal of this campaign was to generate awareness among potential applicants for production licenses and businesses who could support them, about the legitimate new business model created by the MMPR.

17. On December 15, 2012, Health Canada arranged for publication in the Canada Gazette of a notice advising that parties interested in becoming Licensed Producers under the MMPR could seek authorization to conduct research and development activities with cannabis prior to the MMPR coming into force, using existing mechanisms under the *Controlled Drugs and Substances Act* and the *Narcotic Control Regulations.* The notice is available online at *http://canadagazette.gc.ca/rp-pr/p1/2012/2012-12-15/html/notice-avis-eng.html#d111.* A true copy of the Canada Gazette Part I published December 15, 2012 is attached at **Exhibit "C"**.

18. Health Canada also created an outreach plan and made contact with other government organizations, such as Agriculture Canada, Industry Canada, Finance Canada, Business Development Canada, Farm Credit Canada, and Canada Post, as well as with other strategic partners including financial institutions, Provinces, Industry Associations (Insurance Bureau of Canada, Flowers Canada Growers Inc., and Ontario Greenhouse Vegetable Growers) healthcare practitioners, municipalities, law enforcement, fire authorities, and media.

19. In addition, Health Canada developed and implemented an industry engagement strategy that included creating guidance documents about the application process, operating a call centre with trained staff to answer questions from potential applicants, and creating streamlined processes for processing applications, which could be submitted at any time after June 7, 2013.

20. Health Canada also developed and implemented a case management plan for triaging applications for production licenses in an effort to provide for reasonable access to dried marihuana for medical purposes during and following transition to the MMPR. This triage system was created to foster efficient and appropriate approval of qualified applicants and start-up of Licensed Producers.

21. When considering the order in which applications could be processed, Health Canada assesses the applications against a variety of factors including the completeness of the application, and the application's quality: for example, the level of detail provided in respect of good production practices, record keeping and security, and the applicant's general business readiness.

22. A case management approach was also adopted, which involves appointment of case managers to work with applicants to complete the review process and to enhance timely processing of applications.

23. Other significant elements of Health Canada's strategy for providing for reasonable access to a quality supply of dried marihuana for medical purposes include:

a. Providing applicants with "Ready to Build" letters, upon the completion of the paper review process, upon request. These letters advise applicants that if they complete their site build as described in their application, if the site is verified by a pre-licence inspection, and if security clearances are granted, the applicant's licence can be issued. This letter is intended to provide applicants with documentation they may use to make necessary financial and other business-related arrangements; and

b. Providing a "phased licensing process": If an applicant has completed the paper review and met the regulatory standards for cultivation of dried marihuana, Health Canada will inspect and licence that applicant for the cultivation activity only, in order to accelerate production capacity. The applicant could subsequently obtain full licensing upon meeting the further requirements of the MMPR. This means, for example, that applicants who are ready to begin cultivation, but who are not yet set up to meet the storage security requirements under the regulations, could begin to grow marihuana while continuing to complete the requirements for physical storage of dried marihuana.

The Progress of the Licensed Producer Application Process

24. As of February 4, 2014, Health Canada has received 454 Licensed Producer applications:

- 152 applications are at the screening phase (This is the preliminary triage to ensure the completeness of the application;
- 153 applications are at the review phase (This is the in depth review to ensure that all the requirements of the MMPR are met);
- 62 have been returned as incomplete (they may be resubmitted);
- 27 applicants have "ready to build letters";
- 12 applicants are pending pre-licence inspections;
- 6 application is at final review/approval;
- 8 licences have been issued (1 of the 8 is a phased licence);
- 24 applications have been refused; and
- 10 applications have been withdrawn.

Note: as of the date of swearing this affidavit, applications continue to come into the Office of Controlled Substances daily, at an average of 25 applications per week.

25. When a Licensed Producer is ready to begin registering clients, contact information for that Licensed Producer is provided on the Health Canada website.

26. As of January 30, 2014, the Health Canada Website indicated that 6 of the 8 currently Licensed Producers are ready to register clients:

Bedrocan Canada Inc.	1-855-420-7887	info@bedrocan.ca
Canna Farms Ltd.	1-855-882-0988	Info@cannafarms.ca
CanniMed Ltd.	1-855-787-1577	info@cannimed.com
Mettrum Ltd.	1-844-638-8786 (METTRUM)	info@mettrum.com
The Peace Naturals Project Inc	1-888-64-PEACE (73223)	info@peacenaturals.com
Tweed Inc.	1-855-55-TWEED (89333)	hi@tweed.com

27. The collective, projected annual production capacity of the eight currently Licensed Producers is over 31,000 kilograms of dried marihuana. By March 31, 2014, I predict another 12 applicants will be licensed to produce marihuana for medical purposes; these additional applicants' projected annual production capacities will increase the 31,000 kilograms to 45,000 kilograms of dried marihuana annually.

28. I have visited the above Licensed Producer websites and note that as of January 30, 2014, approximately 60 strains of marihuana for medical purposes are available at prices ranging from $5 to $12 per gram, with a number of licensed producers offering discounts to as low as $3.00 per gram for low income users. Attached at **Exhibit "D"** are true copies of the websites for each of the above Licensed Producers.

29. Licensed Producer estimates suggest that as of April 2014, approximately 850 kilograms of dried marihuana will be available for medical use, in addition to any accumulated inventory that has not yet been sold.

The Plan for Transition

30. Health Canada took significant steps to project both demand and available supply of dried marihuana for medical use. In anticipating demand, Health Canada took into account available information on numbers of individuals licenced to use dried marihuana for medical purposes, the upward trend of that number, the daily dosage amounts identified in the most current scientific literature and international practice around dosage, as set out in "Information for Health Care Professionals" available online at http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php and attached at **Exhibit "E"**).

31. The "Information for Health Care Professionals" document, at page iii (see Exhibit "E") states that "Following the most recent update to this document (February 2013), a study was published in the Netherlands tracking data obtained from the Dutch medical cannabis program over the years 2003-2010. The study reported that in a population of over 5,000 Dutch patients using cannabis for medical purposes, the average daily dose of dried cannabis (various potencies) used was 0.68 grams per day (Range: 0.65-0.82 grams per day) (Hazencamp and Heerdink 2013). In addition, information from Israel's medical marihuana program suggests that the average daily amount used by patients was approximately 1.5 grams of dried cannabis per day in 2011-2012 (Health Canada personal communication)."

32. Supply estimates took into account producer forecasts, which Health Canada "risk-adjusted" to account for unforeseen circumstances. By risk adjustment, I mean that the forecasting model discounted producer-estimated production amounts by between 70% and 90%, based on individual applicant factors, such as: access to starting materials, status of financing, relationship with municipality, experience working in a regulated environment, site readiness, and related expertise. These risk factors were adjusted as applicants progressed through the review process.

33. Health Canada has made arrangements with its current contractor, Prairie Plant Systems (PPS), to purchase overstock as a reserve in case of a supply shortfall during the transition period to Licensed Producers. Health Canada has secured between 400-500 kilograms of dried marihuana, which is available for sale now to Canadians whose physician supports their use of dried marihuana for medical purposes. As of January 19, 2014, Health Canada has not yet had to rely on its store of dried marihuana.

34. Further, since the October 1, 2013 cut off for granting new Personal Use and Designated Production licences, there has been a negligible increase in the amount of dried marihuana ordered from Health Canada, so Health Canada continues to accumulate inventory.

35. Health Canada has also explored the possibility of importing marihuana from international sources, and in fact, held discussions with the Netherlands and Israel to that end. Ultimately, Health Canada approved import from the Netherlands of over 100 kilograms of dried marihuana between January and May 2014.

36. In addition, Health Canada has considered the possibility of a collaborative approach among Licensed Producers, which if necessary, could be negotiated to manage demand while supply catches up.

37. Through contingency planning, estimating supply and demand, and facilitating applications from potential Licensed Producers, Health Canada has made significant effort to provide reasonable access to quality dried marihuana for medical use. Both during and after the MMPR transition, Health Canada will continue to monitor supply and demand for this purpose.

38. The specific volume of dried marihuana that may be available in April 2014 is dynamic, because Health Canada receives an average of 25 new Licensed Producer applications per week from applicants with different capacities and in various states of readiness.

39. Health Canada's approach to contingency planning was and is guided by the principle that a legal supply of dried marihuana for medical purposes must be reasonably accessible and that a market of dried marihuana purchasers must exist to support the newly licensed production industry.

40. Failure of the projected market to materialize will negatively affect the commercial viability of commercial suppliers and undermine the implementation of the MMPR.

AFFIRMED BEFORE ME at the City of Ottawa, Province of Ontario, this 7th day of February, 2014.

Notary Public in and for the Province of Ontario

TODD CAIN

This is **Exhibit " A "** referred to in the
Affidavit of **TODD CAIN**
Affirmed before me
at the City of Ottawa,
in the Province of Ontario,
this 7th day of February 2014.

A Notary Public in for the Province of Ontario

This is **Exhibit " B "** referred to in the
Affidavit of **TODD CAIN**
Affirmed before me
at the City of Ottawa,
in the Province of Ontario,
this 7th day of February 2014.

A Notary Public in for the Province of Ontario

This is **Exhibit " C "** referred to in the
Affidavit of **TODD CAIN**
Affirmed before me
at the City of Ottawa,
in the Province of Ontario,
this 7th day of February 2014.

A Notary Public in for the Province of Ontario

This is **Exhibit " D "** referred to in the
Affidavit of **TODD CAIN**
Affirmed before me
at the City of Ottawa,
in the Province of Ontario,
this 7th day of February 2014.

A Notary Public in for the Province of Ontario

This is **Exhibit " E "** referred to in the
Affidavit of **TODD CAIN**
Affirmed before me
at the City of Ottawa,
in the Province of Ontario,
this 7th day of February 2014.

A Notary Public in for the Province of Ontario

This is **Exhibit " A "** referred to in the
Affidavit of **TODD CAIN**
Affirmed before me
at the City of Ottawa,
in the Province of Ontario,
this 7th day of February 2014.

A Notary Public in for the Province of Ontario

TODD R. CAIN

PROFILE

An insightful and driven leader with a rich base of experience covering strategic management, public sector governance and HR gained through direct line experience as well as policy and consulting roles with leading organizations including Ford, GE, Deloitte and the Treasury Board of Canada.

EMPLOYMENT

EXECUTIVE DIRECTOR, MARKET DEVELOPMENT — *2013 to Present*
Health Canada
On executive interchange from the Institute on Governance, led outreach to the private sector to ensure a viable, professional supply base to meet patient needs for medicinal cannabis under new regulations. Collaborate with federal partners, industry, the financial sector, medical researchers, law enforcement and municipal officials on implementation.

VICE-PRESIDENT, PUBLIC GOVERNANCE — *3 years*
The Institute on Governance
Led the Institute's practice in organization effectiveness and governance for crown corporations, core government and non-profits, working with board chairs, CEOs and executive teams to improve governance and performance, as well as leading related research programs.

SENIOR MANAGER, CONSULTING — *4 years*
Deloitte Inc.
Led the national organization design practice as well as local consulting projects for a diverse set of clients on strategy, organizational optimization, talent management, human resources transformation, governance, acquisition integration, compensation, change and process improvements. Developed relationships at senior levels in the federal public service, led sales pursuits and new services development, and research and wrote on topics in organization design and public management.

POLICY DIRECTOR — *2 years*
Treasury Board of Canada
Provided critical analysis and strategic advice to the President of the Treasury Board on policy, governance and management issues in the Federal Government. Consulted with parliamentarians, officials and stakeholders on departmental and government-wide issues. Developed communications plans and materials in support of policy initiatives.

MANAGER, HUMAN RESOURCES — *1 years*
GE Hydro Supply Chain and Compensation and Benefits
Provided strategic HR support to the Global Supply Chain organization of GE Hydro, encompassing 1100 employees in 6 countries, including change management, organization and talent development. Managed global compensation and benefits for entire business, including salary planning and expatriate management.

DIRECTOR, HUMAN RESOURCES & INTEGRATION LEADER *2.5 years*

Led HR for GE's growing, global industrial water treatment equipment company driving organizational change, strategic business initiatives, cost controls, cultural integration and a major recruiting campaign. Key initiatives included international taxation, sales compensation, market driven re-organization, employee retention, acquisition due diligence, analysis and integration. Stock option recipient.

MANAGER, HUMAN RESOURCES *2 years*

GE Energy Services Canada

Managed HR for the Canadian region of multiple business units of GE Energy. Negotiated 7 collective agreements with 6 different unions and was a member of the national GE Canada bargaining team. Led a major upgrade of the leadership team. Assisted in the due diligence and integration of 2 acquisitions. Contributed to a review of the Canadian market for power generation equipment and services. Stock option recipient.

HUMAN RESOURCES ASSOCIATE *4 years*

Ford Motor Company of Canada

Highlights included leading large scale hiring and training programs during plant expansions, merit planning, union relations, numerous automation projects and local and national bargaining in a 5 plant, 6500 employee automotive complex.

RESEARCH ASSISTANT *2 years*

Programs for Employment and Workplace Systems, Cornell University

Researched topics in union-management cooperation and organizational development analysed case studies in creativity and innovation in industrial relations and assisted consultants with training programs in interest-based bargaining.

EDUCATION

Cornell University **Ithaca, NY**

Master of Industrial and Labour Relations

Carleton University **Ottawa, ON**

Bachelor of Public Administration, Highest Honours

PUBLICATIONS

Public Governance Exchange Research Series, IOG, 2010-12

Dr. Schumpeter Comes to the public sector: Creative destruction in public spending, Deloitte, Spring 2008

Closing the gap between policy design and execution, Canadian Government Executive, January 2008

This is **Exhibit " B "** referred to in the
Affidavit of **TODD CAIN**
Affirmed before me
at the City of Ottawa,
in the Province of Ontario,
this 7th day of February 2014.

A Notary Public in for the Province of Ontario

Health Canada / Santé Canada

Healthy Environments and Consumer Safety Branch (HECSB)
Direction générale de la santé environnementale et de la sécurité des consommateurs (DGSESC)

Office of Controlled Substances

GUIDANCE DOCUMENT

APPLICATION TO BECOME A LICENSED PRODUCER UNDER THE *MARIHUANA FOR MEDICAL PURPOSES REGULATIONS*

(Disponible en français)

This guide does not have any official legal status. It is a reference document and appropriate official documents should be consulted.

June 19, 2013

Canada

Pub: 130076

TABLE OF CONTENTS

1. PURPOSE

This Guidance Document is intended to help a potential licensed producer understand how to complete the ***Application to Become a Licensed Producer under the Marihuana for Medical Purposes Regulations*** (the application). Activities that require a licence under the MMPR include:

- possessing, producing, selling, providing, shipping, delivering, transporting, and destroying marihuana;
- possessing and producing cannabis, other than marihuana, solely for the purpose of conducting *in vitro* testing that is necessary to determine the percentages of cannabinoids in dried marihuana;
- selling, providing, shipping, delivering, transporting, and destroying cannabis, other than marihuana, that was obtained or produced solely for the purpose of conducting *in vitro* testing that is necessary to determine the percentages of cannabinoids in dried marihuana.

Other guidance documents and directives are mentioned throughout this document. Please refer to them as you complete your application to be sure that all appropriate information is included.

This is a guidance document only. It is intended to facilitate the process of completing the application. If there is any inconsistency between this document and the *Controlled Drugs and Substances Act* (CDSA) or the *Marihuana for Medical Purposes Regulations* (MMPR), the CDSA and the MMPR will take precedence. The CDSA and the MMPR are available online at http://canada.justice.gc.ca or you can obtain a copy by contacting Government of Canada Publication, Ottawa, Ontario, K1A OS9.

Please note that it is the responsibility of the applicant to ensure that all relevant sections of the applications are completed. Incomplete applications may be returned to the applicant. Priority will be given to complete applications.

2. DEFINITIONS AND ACRONYMS

The terms used in this document are defined in the CDSA and in the MMPR. Please refer to section 2 of the CDSA and section 1 of the MMPR for a complete list of definitions. For ease of reference, the definitions of dried marihuana, marihuana and cannabis have been set out below.

- **"Dried marihuana"** means harvested marihuana that has been subjected to any drying process.

- **"Marihuana"** means the substances referred to as "Cannabis (marihuana)" in subitem 1(2) of Schedule II to the CDSA.

  Please note that this includes the plant itself and parts of the plants (seeds, clippings) as well as dried marihuana.

- **"Cannabis"** means the substance set out in item 1 of Schedule II to the CDSA.

Please note that the term "Cannabis, other than marihuana" in the MMPR is used exclusively to refer to derivatives of cannabis, cannabis preparations and similar synthetic preparations that are used for testing, such as reference standards for delta-9-tetrahydrocannabinol or cannabidiol. These can be obtained or produced solely for the purpose of conducting *in vitro* testing that is necessary to determine the percentages of cannabinoids in dried marihuana.

3. COMPLETING THE APPLICATION TO BECOME A LICENSED PRODUCER UNDER THE *MARIHUANA FOR MEDICAL PURPOSES REGULATIONS*

SECTION 1: Preferred Language of Communication

Please indicate the applicant's preferred language of communication.

SECTION 2: Applicant Name

Who can apply to become a licensed producer under the MMPR?

1. Individual adults of 18 years of age or older who ordinarily reside in Canada; or
2. Corporations that have a head office or a branch office in Canada and whose officers and directors are all adults.

2.a. Applicant Name

This section should be completed by both individual applicants and, in the case of corporations, their authorized corporate representatives.

Please provide the applicant's full legal name and any other name(s) registered with the province, under which the individual intends to identify himself or herself or conduct the activities for which the licence is sought. Please also provide contact information for the applicant, as well as the applicant's gender and date of birth.

2.b. Corporate Applicant

If the applicant is a corporation, please complete section 2.b. of the application. Please provide the legal name(s) of the corporation, and other name registered with a province, under which the corporation intends to identify itself or conduct the activities for which the licence is sought.

As part of the application, the applicant will be required to provide proof of the corporation's name in the form of a photocopy of a certificate of incorporation and, if applicable, a copy of any document filed with the province that states the corporation's name.

A corporate applicant will also be required to provide a list of its officers and directors of the corporation, including the full legal name, date of birth, and gender of each individual, and whether each officer and director holds a valid security clearance.

SECTION 3: Proposed Personnel

The applicant must designate personnel who will oversee licensed activities at the site. The designated persons must be adults, and must be familiar with the CDSA and its regulations, and the *Food and Drugs Act*.

3.a. Proposed Senior Person in Charge (Senior PIC)

The applicant must designate a Senior Person in Charge (Senior PIC) who has overall responsibility for management of the activities carried out by the licensed producer under their licence at their proposed site. Note: The applicant can be the Senior PIC.

The Senior PIC is considered the representative of the applicant and must have the authority, as an authorized official, to bind the applicant.

Please specify the proposed Senior PIC's full name, title (if applicable), gender and date of birth. Please also provide the telephone number, facsimile number, and e-mail address of the Senior PIC in order to facilitate contact.

3.b. Proposed Responsible Person in Charge (RPIC)

The applicant must designate a Responsible Person in Charge (RPIC) who will work at the site and will be responsible for supervising licensed activities, and for ensuring that the activities comply with the CDSA, its regulations and the *Food and Drugs Act*.

Please provide the proposed RPIC's full name, gender and date of birth. Please also provide the proposed RPIC's title and proposed work hours.

Note: The proposed Senior PIC can also be the proposed RPIC.

3.c. Proposed Alternate Responsible Person in Charge (A/RPIC)

The applicant may designate one or more Alternate Responsible Persons in Charge (A/RPIC) who will work at the site and have the authority to act for the Responsible Person in Charge (RPIC) when that person is absent.

Please provide the full name, gender and date of birth for the proposed A/RPIC(s). Please also provide the title and proposed work hours for the proposed A/RPIC(s).

If the applicant designates more than one A/RPIC, please indicate the ranking of each A/RPIC (i.e. first alternate, second alternate, etc.).

3.d. Proposed Persons Authorized to Place Orders for Cannabis on Behalf of the Applicant

In order to place orders for cannabis on behalf of the applicant, individuals must be authorized. For example, if you want to order cannabis from another Licensed Producer, the employee placing the order on your behalf first must be authorized before the order can be placed.

Please provide the full name of each individual to be authorized to place orders for cannabis, along with his or her gender. These individuals may include the Senior Person in Charge, the Responsible Person in Charge, and the Alternate Responsible Person(s) in Charge.

SECTION 4: Security Clearance

The following individuals are required to have a valid security clearance:

- An individual applicant
- All officers and directors of a corporate applicant (as identified in section 2.b.)
- The proposed Senior Person in Charge (as identified in section 3.a.)
- The proposed Responsible Person in Charge (as identified in section 3.b.)
- The proposed Alternate Person(s) in Charge (as identified in section 3.c.)

The individuals identified above **must** hold a valid security clearance. A producer's licence will not be issued if all the security clearances required under the MMPR have not been granted.

If any of these individuals already hold a valid security clearance, please attach the confirmation of the security clearance to the application.

If any of the individuals listed above do not already hold a valid security clearance, they will be required to complete the **Security Clearance Application Form**. The form can either be sent with the completed application, or it can be sent separately. If sent separately, please attach a note to clearly indicate under which name and for which site the application was made. The **Security Clearance Application Form** can be found online at: http://www.hc-sc.gc.ca/dhp-mps/marihuana/info/securit-eng.php

As part of the Security Clearance Application process, each of the individuals identified above will be required to complete the **Security Clearance Fingerprint Third Party Consent to Release Personal Information** form that will allow a Canadian police force or a fingerprinting company accredited by the RCMP to submit fingerprints to the RCMP for the purposes of a criminal record check. A list of agencies accredited by the RCMP can be found at: http://www.rcmp-grc.gc.ca/rtid-itr/vulner-eng.htm. The **Security Clearance Fingerprint Third Party Consent to Release Personal Information** form can be found online at http://www.hc-sc.gc.ca/dhp-mps/marihuana/info/third_party-tierce_partie-eng.php. Health Canada does not need to be provided with a copy of this consent form.

Note: Applications will not be processed until all completed Security Clearance Application forms associated with this application have been received.

SECTION 5: Activities and Substances to be specified on the Licence

5.a. Activities with Marihuana

In this section, the applicant must indicate: the type of activities they propose to carry out; a description of the substances for each activity (i.e., whether the activities involve dried marihuana, marihuana plants and/or marihuana seeds); the building name and address where each of the activities will be taking place; and the purposes for conducting those activities.

The applicant may request a licence to conduct any or all of the following activities for dried marihuana and/or marihuana, other than dried marihuana, which means the plant itself or seeds:

a) Possession;
b) Sale or Provision;

c) Shipping, Transportation or Delivery;
d) Destruction; and/or
e) Production

Note: If a licence allows possession of marihuana it is not necessary to have the licence allow the holder to purchase marihuana, be it dried marihuana, the plant itself or seeds.

For example:

- If you want to produce dried marihuana, the purpose could be to produce for the purpose of selling or providing to registered clients.
- If you wish to ship marihuana, the purpose could be to ship to registered clients, another licensed producer, or a licensed dealer for testing.

5.a.i. Maximum Quantity of Dried Marihuana to be Produced (if applicable)

Please indicate the maximum quantity of dried marihuana (net weight in kilograms) that you intend to produce and the production period. The maximum quantity and specified period will be indicated on your licence.

5.a.ii. Maximum Quantity of Dried Marihuana to be Sold or Provided to Persons Referred to in the MMPR (if applicable)

Please indicate the maximum quantity of dried marihuana (net weight in kilograms) that you intend to sell or provide to eligible persons (i.e. a registered client, an individual who is responsible for a registered client, a hospital employee or person to whom an exemption relating to dried marihuana has been granted under s.56 of the CDSA). Please also specify the period in which that quantity is to be sold or provided.

Note: In your application you do not need to indicate the amount you intend to sell or provide to another licensed producer, to a licensed dealer, or to the Minister. However, any sales or provision of cannabis to another licensed producer, licensed dealer or the Minister requires a written order and for records of that transaction to be kept.

5.b. Activities with Cannabis (*in vitro* testing)

Note: You only need to complete this section if you intend to conduct activities with cannabis derivatives, preparations and similar synthetic preparations, other than marihuana, necessary to conduct *in vitro* testing (for example, reference standards for delta-9-tetrahydrocannabinol or cannabidiol) to determine the percentages of cannabinoids in dried marihuana.

In this section, the applicant must indicate: the type of activities they propose to carry out; a description of the substances for each activity; the building name and address where each of the activities will be taking place; and the purposes for conducting those activities.

The applicant may request a licence to conduct any or all of the following activities with cannabis, other than marihuana (intended for conducting *in vitro* testing):

a) Possession;
b) Sale or Provision;
c) Shipping, Transportation or Delivery;
d) Destruction; and/or
e) Production

You can possess and produce cannabis, other than marihuana, solely for the purpose of conducting *in vitro* testing that is necessary to determine the percentages of cannabinoids in dried marihuana. You can also sell, provide, ship, deliver, transport and destroy cannabis, other than marihuana, obtained or produced solely for the purpose of conducting *in vitro* testing that is necessary to determine the percentages of cannabinoids in dried marihuana.

For example:

- If you intend to possess derivatives of cannabis, such as THC or cannabidiol found in reference standards, the purpose could be to conduct *in vitro* testing of dried marihuana you produce to determine the percentages of cannabinoids in dried marihuana.
- If you intend to produce derivatives of cannabis from marihuana, the purpose could be to conduct *in vitro* testing of dried marihuana you produce to determine the percentages of cannabinoids in dried marihuana.
- If you intend to provide cannabis, other than marihuana, the purpose could be to provide solely for the purpose of determining the percentages of cannabinoids in dried marihuana (for example, providing marihuana produced to another licensed producer for testing).

SECTION 6: Proposed Site Information

Site Information

The MMPR defines a "site" as (a) a building or a place in a building used by a licensed producer; or (b) an area occupied exclusively by buildings used by a licensed producer.

Please provide the address, telephone number and, if applicable, the facsimile number and email address of the proposed site. If the site's mailing address is different than the site's municipal address, please provide the site's mailing address.

The proposed site must be located indoors and **must not** be a dwelling-place (i.e. a place of residence).

The proposed site may consist of an area occupied **exclusively** by buildings used by the applicant. If you intend to conduct licensed activities at more than one site, a separate application must be submitted for each site.

Regardless of the scope of your licensed activities, you will need a separate application for each physical site where you are proposing to undertake activities licensed under the MMPR.

Note: Your site must be available for a pre-licence inspection by Health Canada for compliance with the MMPR.

Building Information

If the proposed site is an area comprised of more than one building, please provide information on each building on the site. Please provide, the building name (if applicable), street address, city, telephone and, if applicable, facsimile numbers, and email address.

Example:

If a proposed site is an area which contains three buildings, you would need to provide information on the site, as well as all three buildings on the site. All three buildings on the site must be used by the applicant only.

If there are buildings on a site that are not exclusively used by the applicant, then these buildings must be treated as separate sites. In this instance, a separate application would be required for each site.

Note: The applicant is encouraged to use their site floor plan, as required under Section 8: Proposed Site and Physical Security, to clarify their site and building information.

SECTION 7: Ownership of Property

If the applicant is the owner of the entire proposed site, the declaration in this section must be signed by the proposed Senior Person in Charge (Senior PIC) as the person authorized to bind the applicant.

If the proposed site, or any portion of the proposed site, is not owned by the applicant, the declaration in Appendix A must be completed. To complete Appendix A, the applicant must provide the full address of the proposed site, or any portion of the proposed site, for which the applicant is not the owner. The applicant must also provide a description of the activities that will be conducted at that site. The owner/co-owners of the site must then complete and sign the declaration, stating that they: are the owner/co-owner of the proposed site; are fully aware of the activities that the applicant proposes to conduct at that site; and consent to those activities being carried out at the site.

If the proposed site, or any portion of it, is owned by more than one individual, the declaration in Appendix A of the application form must be signed by each owner.

Appendix A must be submitted with applications where the applicant proposes to undertake licensed activities on property not owned by the applicant.

SECTION 8: Proposed Site and Physical Security

The applicant must comply with the site and physical security requirements under the MMPR. Please attach a detailed description of the security measures and floor plans of the site, including each of the buildings within the proposed site where any licensed activities are to be conducted. The applicant must also include floor plans for the site, including each building of the proposed site where proposed licensed activities are to be conducted.

Your proposed site must be designed in a manner that prevents unauthorized access.

To determine the security measures required for proposed licensed activities, please refer to the *Marihuana for Medical Purposes Regulations*, the *Guidance Document – Building and Production Security Requirements for Marihuana for Medical Purposes* at: http://www.hc-sc.gc.ca/dhp-mps/marihuana/info/bp-securit-eng.php, and the Health Canada *Directive on Physical Security Requirements for Controlled Substances at:* http://www.hc-sc.gc.ca/hc-ps/pubs/precurs/dealers-distrib/phys_securit_directive/index-eng.php.

The MMPR set out physical security requirements that are necessary to secure sites where licensed producers conduct activities with marihuana, other than storage. The Guidance Document – *Building and Production Security Requirements for Marihuana for Medical Purposes* provides technical details on how to meet these security requirements.
For storage, Health Canada's *Directive on Physical Security Requirements for Controlled Substances* establishes security requirements for the storage of all controlled substances including dried marihuana, marihuana seeds, and cannabis (for the purposes of conducting *in vitro* testing only) by licensed producers. The applicant is encouraged to follow the *Directive on Physical Security Requirements for Controlled Substances,* as much as possible, in developing the storage elements of their plan.

Please note that the level of security for storage may be different for each building on the proposed site. Please indicate on the building's floor plan the proposed level of security for storage of that building in accordance with the Directive listed above.

The proposed security measures must meet the requirements set out in the *Directive on Physical Security Requirements for Controlled Substances* and in the MMPR, including:

- The perimeter of the licensed producer's site must be visually monitored at all times by visual recording devices to detect attempted or actual unauthorized access.
- The areas within a site where cannabis is present must be visually monitored at all times by visual recording devices to detect illicit conduct.
- The visual recording devices must be capable of recording attempted or actual unauthorized access in a visible manner.
- The perimeter of the site and areas within a site where cannabis is present must be secured at all times by an intrusion detection system capable of detecting attempted and actual unauthorized access to or movement in the site, or tampering with the system.
- The intrusion detection system must be monitored at all times by personnel who can determine the appropriate steps to take in response to any detected activity that is unauthorized.
- In the case of any detected activity, the personnel must record the date and time of the detected matter and the measures taken in response to it. Personnel must also record the date and time when measures were taken.
- Access to areas within a site where cannabis is present must include physical barriers that prevent unauthorized access and must be limited to personnel who require access to the areas to perform their work responsibilities. Records must be kept of each person entering or exiting these areas.
- All areas within a site must be equipped with a system that filters air to prevent the escape of odours and, if present, pollen.

Note: Before a licence can be issued, your compliance with the site and physical security requirements under the MMPR and Health Canada *Directive on Physical Security Requirements for Controlled Substances* will be verified through a pre-licence inspection conducted by Health Canada.

SECTION 9: Notice to Local Government, Police and Fire Authorities

Prior to submitting an application to become a licensed producer of marihuana for medical purposes, the applicant must provide a written notice to local authorities to inform them of their

intention to submit an application. The notice must include the applicant's name, the activities for which the licence is sought (i.e. that activities are to be conducted in respect of cannabis), the site address (and of each building on the site, if applicable) at which the applicant proposes to conduct those activities, as well as the date when the application will be submitted to Health Canada.

In the application to become a licensed producer of marihuana for medical purposes, please identify the name, title and address of the senior official for each of the following local authorities, as well as the date when the notification was provided:

- the local police force or Royal Canadian Mounted Police detachment responsible for providing policing services to the area in which the proposed site is located;
- the local fire authority of that area; and
- the local government (for example, municipality) of that area.

The Senior Person in Charge must sign the declaration in this section confirming that they have provided the required notice to local authorities. A copy of each notice must be provided with the application.

SECTION 10: Quality Assurance Pre-Licensing Report

A licensed producer must have an employee designated as a quality assurance person who is responsible for assuring the quality of the dried marihuana, before it is made available for sale. This employee must have the training, experience and technical knowledge related to the proposed licensed activities and the requirements of the MMPR.

The applicant must submit a document signed and dated by the quality assurance person that includes:

i. a description of the quality assurance person's qualifications in respect of the proposed licensed activities and the requirement of the MMPR; and
ii. a report establishing that the buildings, equipment and proposed sanitation program to be used in conducting the proposed activities referred in the MMPR comply with the regulatory requirements.

The accuracy of the information contained in the report will be verified by Health Canada inspectors during the pre-licence inspection of the proposed site.

For more information on quality requirements, please refer to the *Guidance Document – Technical Specifications for Testing Dried Marihuana for Medical Purposes at: http://www.hc-sc.gc.ca/dhp-mps/marihuana/info/techni-eng.php.*

SECTION 11: Record Keeping

The applicant must submit a detailed description of their proposed record keeping methods. This must include a description of the process that will be used for recording transactions relating to licensed activities, including maintaining appropriate records of transactions and dealings with both suppliers and clients.

The method of record keeping proposed by the applicant must permit compliance with the requirements of Part 6 of the MMPR. The record keeping must allow for the reconciliation of orders for cannabis (including marihuana) and shipments and inventories of cannabis (including marihuana).

Note: The Minister of Health can request that a licensed producer provide records, documents and information referred to in the MMPR in the form and at the time specified by the Minister.

SECTION 12: Declarations and Attestations

The declarations and attestations in the application form must be signed and dated by the proposed Senior Person in Charge.

SECTION 13: Submission

Please submit your completed application to become a Licensed Producer under the *Marihuana for Medical Purposes Regulations*, including all applicable attachments by mail to:

Controlled Drugs Section
Licences and Permits Division
Office of Controlled Substances
Controlled Substances and Tobacco Directorate
Health Canada
150 Tunney's Pasture Driveway, Tunney's Pasture, A.L.: 0300B
Ottawa, ON K1A 0K9

All relevant sections of the application form must be completed and all required documents must be submitted. An incomplete application will not be processed. If your application is incomplete, it may be returned to you.

A Health Canada representative is available to assist you if you have any questions pertaining to these requirements and the application process. You can send us your questions by email at MMPR-RMFM@hc-sc.gc.ca or call us at 1-866-337-7705.

APPLICATION TO BECOME A LICENSED PRODUCER UNDER THE *MARIHUANA FOR MEDICAL PURPOSES REGULATIONS* (MMPR)

(Disponible en français)

For guidance on completing this application please refer to the *Guidance Document: Application to Become a Licensed Producer under the Marihuana for Medical Purposes Regulations*. Note: An incomplete application may be returned to you.

1. PREFERRED LANGUAGE OF COMMUNICATION

English ☐ French ☐

2. APPLICANT

2.a. Applicant Name

Surname of Individual Applicant or Authorized Corporate Representative					
Given Name(s) of Individual Applicant or Authorized Corporate Representative					
Other registered name(s) [1]					
Title (if applicable)					
Gender	M ☐ F ☐		Date of Birth (YYYY/MM/DD)		
Street Address					
City		Province		Postal Code	
Telephone No.	( ) -		Fax No. (if applicable)	( ) -	
Email					

[1] Any other name registered with a province, under which the individual intends to identify himself or herself or conduct the activities for which the licence is sought.

Licence is sought for: ☐ an individual **-or-** ☐ a corporation

2.b. Corporation

For a corporation, please specify the legal name of the corporation and any other name registered with the province under which the applicant intends to identify itself.

Legal name	
Other registered name (s) [2]	

[2] Any other name registered with a province, under which the corporation intends to identify itself or conduct the activities for which the licence is sought.

Please attach the following to the application form:

1. A list indicating the full (legal) name, date of birth and gender of each of the corporation's officers and directors, and whether each officer and director holds a valid security clearance.

   List of directors and officers attached: ☐

2. A copy of the certificate of incorporation or other constituting instrument.

   Certificate attached: ☐

3. **If applicable**, a copy of any document that states the applicant's name that has been filed with the province where the proposed site is located. This includes any document that references any other name registered with the province, under which the applicant intends to identify itself or conduct the proposed activities.

   Document(s) attached: ☐

3. PROPOSED PERSONNEL

3.a. PROPOSED SENIOR PERSON IN CHARGE (SENIOR PIC)

The Senior Person in Charge will have overall responsibility for management of the activities carried out by the licensed producer under their licence at their site — who may, if appropriate, be the licensed producer. Please identify the proposed Senior Person in Charge. The Senior Person in Charge will have the authority to bind the applicant.

Surname		Given Name(s)	
Other Title			
Gender	M ☐ F ☐	Date of Birth (YYYY/MM/DD)	
Telephone No.	( ) -	Fax No. (if applicable)	( ) -
Email			

3.b. PROPOSED RESPONSIBLE PERSON IN CHARGE (RPIC)

The Responsible Person in Charge will work at the licensed producer's site and have responsibility for supervising the activities with respect to cannabis conducted at that site by the licensed producer under their licence, and for ensuring that the activities comply with all relevant Acts and regulations. This person may be the same as the Senior Person in Charge.

Surname		Given Name(s)	
Gender	M ☐ F ☐	Date of Birth (YYYY/MM/DD)	
Proposed Schedule – Work Hours and Days (e.g. 8am – 4pm, Mon – Fri)			
Other Title			

3.c. PROPOSED ALTERNATE RESPONSIBLE PERSON IN CHARGE (A/RPIC)

The applicant may designate one or more Alternate Responsible Person in Charge to work at the proposed site and replace the Responsible Person in Charge when that person is absent. The Alternate Responsible Person in Charge will work at the licensed producer's site, in the absence of the RPIC, and have responsibility for supervising the activities with respect to cannabis conducted at that site by the licensed producer under their licence and for ensuring that the activities comply with all relevant Acts and regulations.

If more than one A/RPIC is proposed, additional pages must be attached for each one. Check here if additional pages are included: ☐

Number of A/RPIC(s) you are submitting:

Proposed A/RPIC:

Surname		Given Name(s)	
Gender	M ☐ F ☐	Date of Birth (YYYY/MM/DD)	
Proposed Schedule – Work Hours and Days (e.g. 8am – 4pm, Mon – Fri)			
Ranking (e.g. 1st A/RPIC, 2nd A/RPIC, etc.)			
Other Title			

3.d. PROPOSED PERSONS AUTHORIZED TO PLACE ORDERS FOR CANNABIS ON BEHALF OF THE APPLICANT

Only individual(s) on this list will be authorized to place orders for cannabis on behalf of the applicant. Attach additional pages if required.

Check here if additional pages are included: ☐

Surname	Given Name(s)		Gender
1)			M ☐ F ☐
2)			M ☐ F ☐
3)			M ☐ F ☐
4)			M ☐ F ☐
5)			M ☐ F ☐

4. SECURITY CLEARANCE

The following individuals are required to have a valid security clearance:

- An individual applicant
- All officers and directors of a corporate applicant (as identified in section 2.b.)
- The proposed Senior Person in Charge (as identified in section 3.a.)
- The proposed Responsible Person in Charge (as identified in section 3.b.)
- The proposed Alternate Person(s) in Charge (as identified in section 3.c.)

The individuals identified above **must** hold a valid security clearance. A producer's licence will not be issued if all the security clearances required under the MMPR have not been granted.

If any of these individuals already hold a valid security clearance, please attach the confirmation of the security clearance to the application.

If any of the individuals listed above do not already hold a valid security clearance, they will be required to complete the **Security Clearance Application Form**. The form can either be sent with the completed application, or it can be sent separately. If sent separately, please attach a note to clearly indicate under which name and for which site (if applicable) the application was made. The **Security Clearance Application Form** can be found online at: http://www.hc-sc.gc.ca/dhp-mps/marihuana/info/securit-eng.php

Note: Applications will not be processed until all completed Security Clearance Application forms associated with this application have been received.

As part of the Security Clearance Application process, each of the individuals identified above will also be required to complete the **Security Clearance Fingerprint Third Party Consent to Release Personal Information** form that will allow a Canadian police force or a fingerprinting company accredited by the RCMP to submit fingerprints to the RCMP for the purposes of a criminal record check. A list of agencies accredited by the RCMP can be found at: http://www.rcmp-grc.gc.ca/rtid-itr/vulner-eng.htm. The Security Clearance Fingerprint Third Party Consent to Release Personal Information form can be found online at http://www.hc-sc.gc.ca/dhp-mps/marihuana/info/third_party-tierce_partie-eng.php. Health Canada does not need to be provided with a copy of this consent form.

	Already holds a security clearance:	Completed Security Clearance Application Form:	Completed Security Clearance Fingerprint Third Party Consent to Release Personal Information form:
Individual Applicant	☐ attached	☐ attached ☐ to follow	☐ submitted to a Canadian police force or a fingerprinting company accredited by the RCMP
Corporate Applicant (Officers and Directors)	☐ attached	☐ attached ☐ to follow	☐ submitted to a Canadian police force or a fingerprinting company accredited by the RCMP
Senior Person in Charge	☐ attached	☐ attached ☐ to follow	☐ submitted to a Canadian police force or a fingerprinting company accredited by the RCMP
Responsible Person in Charge	☐ attached	☐ attached ☐ to follow	☐ submitted to a Canadian police force or a fingerprinting company accredited by the RCMP
Alternate Person(s) in Charge	☐ attached	☐ attached ☐ to follow	☐ submitted to a Canadian police force or a fingerprinting company accredited by the RCMP

5. ACTIVITIES AND SUBSTANCES TO BE SPECIFIED ON THE LICENCE

5.a. ACTIVITIES WITH MARIHUANA

Please check the box(es) of proposed activities that you intend to carry out using **marihuana.** Please also indicate the: substance description; building where the activities will take place; and purpose for conducting each of the activities.

Activity	✓	Substance Description[1]	Building Name and Address[2]	Purpose
a) Possession	☐			
b) Sale or Provision	☐			
Please refer to the MMPR for information about to whom you can sell or provide.				
c) Shipping, Transportation or Delivery	☐			
d) Destruction	☐			
e) Production	☐			

NOTES:

1. Substance Description: Specify whether the activities involve dried marihuana, marihuana plants or seeds.
2. Building: Please ensure this information corresponds to the building information provided in section 6 of this form.

5.a.i. Quantity of Dried Marihuana to be Produced (if applicable)

Please indicate the maximum quantity (expressed as the net weight in kilograms) of dried marihuana to be produced and the production period.

Quantity of dried marihuana to be produced (kg)	Production Period(s) involved

5.a.ii. Quantity of Dried Marihuana to be Sold or Provided to Eligible Persons Under the MMPR (if applicable)

Please indicate the maximum quantity (expressed as the net weight in kilograms) of dried marihuana to be sold or provided to eligible persons and the period in which that quantity is to be sold or provided.

Quantity of dried marihuana to be sold or provided (kg)	Period(s) involved

5.b. ACTIVITIES WITH CANNABIS, OTHER THAN MARIHUANA

Complete this section if you intend to conduct activities with cannabis derivatives, preparations and similar synthetic preparations, other than marihuana (e.g. in order to conduct *in vitro* testing to determine the percentages of cannabinoids in dried marihuana).

Please check the box(es) of proposed activities that you intend to carry out using **cannabis, other than marihuana.** Please also indicate the: substance description; building where the activities will take place; and purpose for conducting each of the activities.

I do not intend to conduct activities with cannabis, other than marihuana: ☐

Activity	✓	Substance Description[1]	Building Name and Address[2]	Purpose
a) Possession	☐			
b) Sale or Provision Please refer to the MMPR for information about to whom you can sell or provide.	☐			
c) Shipping, transportation or delivery	☐			
d) Destruction	☐			
e) Production	☐			

NOTES:

1. Substance Description: Specify the cannabis derivatives, preparations or similar synthetic preparations to be used (e.g. delta 9-tetrahydrocannabinol or cannabidiol).
2. Building: Please ensure this information corresponds to the building information provided at section 6 of this form.

6. PROPOSED SITE INFORMATION

If you intend to conduct licensed activities at more than one site, a separate application must be completed for each site.

Site Information:

Street Address					
City		Province		Postal Code	
Telephone No.	( ) -		Fax No. (if applicable)	( ) -	
Email Address (if applicable)					

Mailing Address: Same as above ☐

Street Address					
City		Province		Postal Code	

Building Information (if applicable):

If the proposed site is comprised of more than one building in which proposed activities are to be conducted, please provide information on each building. For multiple buildings, attach additional sheets as required.

Check here if additional pages are attached: ☐

Number of buildings included: _____

Building Name (if applicable)					
Street Address					
City		Province		Postal Code	
Telephone No.	( ) -	Fax No. (if applicable)	( ) -		
Email (if applicable)					

Mailing Address: Same as above ☐

Street Address					
City		Province		Postal Code	

7. OWNERSHIP OF PROPERTY

If the applicant is the owner of the **entire** proposed site, the declaration in section 7.a. is to be signed by the proposed Senior Person in Charge (Senior PIC).

If the proposed **site or any portion of the site is not owned by the applicant**, a declaration signed and dated by the owner(s) of the site or each portion of the site must be submitted along with this application consenting to the use of it by the applicant for the proposed activities. (See Appendix A)

Appendix A attached to this form: ☐

7.a. Applicant and Site Owner's Declaration

I hereby declare that the entire proposed site, mentioned herein within this application, on which the proposed activities are to be carried out, is entirely owned by the applicant for this license under the *Marihuana for Medical Purposes Regulations.*

Surname of site's Senior PIC		Given Name(s)	
Other Title (e.g. President)			
Signature of the site's Senior PIC:		Date: (YYYY/MM/DD)	

8. PROPOSED SITE AND PHYSICAL SECURITY

Please attach a detailed description of the **security measures and floor plans of the site**, including each of the building(s) within the proposed site within which any licensed activities are to be conducted:

Description of security measures attached ☐

Floor Plan of the site attached ☐

Floor plan(s) for the building(s) attached ☐

Note: Any licensed activities proposed to be undertaken at any proposed site must comply with the requirements *Marihuana for Medical Purposes Regulations* and the Health Canada *Directive on Physical Security Requirements for Controlled Substances* at http://www.hc-sc.gc.ca/hc-ps/pubs/precurs/dealers-distrib/phys_securit_directive/index-eng.php. A security level must be established for each building where cannabis, other than marihuana plants, will be stored.

Please also refer to the *Guidance Document – Building and Production Security Requirements for Marihuana for Medical Purposes* at: http://www.hc-sc.gc.ca/dhp-mps/marihuana/info/bp-securit-eng.php for assistance in determining the security measures required based on the proposed licensed activities to be conducted at the proposed site.

9. NOTICE TO LOCAL GOVERNMENT, POLICE AND FIRE AUTHORITIES

Before submitting this application, a notice that includes the proposed activities to be conducted with cannabis and the address of the site(s) and of each building within the site(s) must be provided to a senior official of the local police, local fire authority and local government.

Please identify below the names of the senior officials within your local police, local fire authority and local government to whom you have provided notifications. Please also attach a copy of each notice to this application.

Copies of all the notices are attached ☐

Police Force

Local authority:	
Name of senior official:	
Title:	
Address:	
Date provided:	

Fire Authority

Local authority:	
Name of senior official:	
Title:	
Address:	
Date provided:	

Local Government (e.g. Municipality)

Local authority:	
Name of senior official:	
Title:	
Address:	
Date provided:	

DECLARATION to be completed by the Senior Person in Charge

I hereby declare that written notices containing the information referred to in this application regarding proposed activities regulated under the MMPR have been provided to the senior official of the local authorities listed above:

Surname (Senior PIC)		Given Name(s)	
Other Title (e.g. President)			
Signature of Senior PIC:		Date: (YYYY/MM/DD)	

10. QUALITY ASSURANCE PRE-LICENSING REPORT

The applicant must submit a document signed and dated by the proposed quality assurance person that includes:

i. a description of the quality assurance person's qualifications in respect of the proposed licensed activities and the requirements of the MMPR; and,
ii. a report establishing that the buildings, equipment and proposed sanitation program to be used in conducting the proposed activities referred in the MMPR comply with regulatory requirements.

Note: The accuracy of the information in the report will be verified by Health Canada inspectors during the pre-licence inspection of the proposed site.

Document signed and dated by the proposed quality assurance person attached: ☐

11. RECORD KEEPING

Please provide in an attachment a detailed description of your proposed record keeping methods. Your proposed record keeping methods must comply with and will be evaluated for compliance with Part 6 of the MMPR.

If available, you may choose to also submit examples of the documents you are planning to use to ensure proper record keeping.

A detailed description of proposed record-keeping methods is attached: ☐

Optional: Example(s) of proposed record-keeping document(s) is attached: ☐

12. DECLARATIONS AND ATTESTATIONS

The following declarations and attestations must be signed and dated by the Senior Person in Charge.

I hereby declare that the proposed Senior Person in Charge (Senior PIC), the proposed Responsible Person in Charge (RPIC), and if applicable, the proposed Alternate Responsible Person(s) in Charge (A/RPIC) are familiar with the provisions of the *Controlled Drugs and Substances* Act and its regulations and the *Food and Drugs Act* that will apply to this licence.

I hereby declare that the entire proposed site, mentioned herein within this application, on which the proposed activities are to be carried out, is not a dwelling-place.

I hereby attest that all of the information and documents submitted in support of the application are, to the best of my knowledge, correct and complete.

I hereby attest that I have the authority to bind the applicant.

Surname of Senior PIC		Given Name(s)	
Other Title (e.g. President)			
Signature of Senior PIC:		Date: (YYYY/MM/DD)	

13. SUBMISSION

Please take note that all mandatory information and documents requested must be provided to avoid delay of processing this application. Your application may be returned to you if it is incomplete. Please send the completed Application Form and accompanying documents to the Office of Controlled Substances at the following address:

Health Canada
A.L.: 0300B
Ottawa, ON
KIA 0K9

A Health Canada representative is available to assist you if you have any questions pertaining to these requirements and the application process. You can send us your questions by email at MMPR-RMFM@hc-sc.gc.ca or call us at 1-866-337-7705.

APPENDIX A

CONSENT BY OWNER TO UTILIZE SITE

If the proposed site, or any portion of the site, identified below is not owned by the applicant, this declaration is to be signed and dated **by the owner of the site** (or each portion of the site). The owner must consent to the use of the site by the applicant for the proposed activities with cannabis.

If there are multiple owners, each owner must consent to the use of the site by the applicant for the proposed activities with cannabis using part (2) b) of this Appendix. Please attach additional pages as needed.

Check here if additional pages are attached: ☐

(1) To be completed by the applicant:

Please provide a brief description of the activities to be conducted on the proposed site or any portion of the site for which this consent is being requested.

Description of Activities to be Conducted with Cannabis on the Proposed Site

Location of proposed site for which consent is being requested:

Street Address					
City		Province		Postal Code	

(2) To be completed by site owner(s):

(2) a) Sole owner

I hereby declare that I am the sole owner of the proposed site listed in section (1) of this Appendix and that I am fully aware of and consent to the activities with cannabis described in section (1) of this Appendix being conducted on this site.

Signature: _____ Date: _____
(YYYY/MM/DD)

Print Full Name: _____

(2) b) Joint Owner(s)

Note: If the site is co-owned, please provide the name and address for each property owner.

Property Co-owner

Full Name:	
Address:	

Property Co-owner

Full Name:	
Address:	

Property Co-owner

Full Name:	
Address:	

Property Co-owner

Full Name:	
Address:	

I hereby declare that I am a co-owner of the proposed site listed in section (1) of this Appendix and that I am fully aware of and consent to the activities with cannabis described in section (1) of this Appendix being conducted on this site.

Property co-owner's signature: _____

Print Full Name: _____

Date: _____
(YYYY/MM/DD)

Property co-owner's signature: _____

Print Full Name: _____

Date: _____
(YYYY/MM/DD)

Property co-owner's signature: _____

Print Full Name: _____

Date: _____
(YYYY/MM/DD)

Property co-owner's signature: _____

Print Full Name: _____

Date: _____
(YYYY/MM/DD)

Check here if additional pages are included ☐

Health Canada Santé Canada

Canada

SECURITY CLEARANCE APPLICATION FORM

MARIHUANA FOR MEDICAL PURPOSES REGULATIONS (MMPR)

Privacy Notice Statement

The information you provide on this form is required by Health Canada for the purpose of having a security screening assessment conducted as part of the application process for a licence to produce marihuana for medical purposes. This Notice explains the purposes of the collection and use of the personal information you provide on this form. The collection and use of your personal information is in accordance with the federal *Privacy Act* and collected under the authority of the *Marihuana for Medical Purposes Regulations* (MMPR). The personal information collected is retained in Health Canada Personal Information Bank number HC PPU 073 and will be processed by the Office of Controlled Substances (OCS). Security clearance is a requirement under the MMPR for issuance of a licence to produce marihuana for medical purposes. A refusal to provide the information requested on this form will result in the refusal of the application. The information collected by Health Canada will be disclosed to the Royal Canadian Mounted Police (RCMP) for the purpose of conducting a criminal activity check. In some cases, personal information may be disclosed without your consent for purposes not outlined here pursuant to subsection 8 (2) of the *Privacy Act*. The *Privacy Act* states that you have the right to access your personal information and request changes to incorrect information or make changes to the information disclosed in this form.

ADMINISTRATIVE INFORMATION (To be completed by Department)		
Surname	**New ◯ Update ◯**	**Request #**
Individual applicant / Company Name:		
Position of the Person for the Individual applicant/Company:		

Part A - Requirements Checklist (To be submitted by applicant)

◯ All 5 pages of the application form completed and signed.
◯ A copy of a valid piece of photo identification issued by the government of Canada or a province or a copy of the applicant's passport that includes the passport number, country of issue, expiry date and the applicant's photograph.
◯ Applicant's Fingerprints – Please confirm that you have submitted the Security Clearance Fingerprint Third Party Consent to Release Personal Information Form to a Canadian police force or private accredited fingerprinting agency accredited by the RCMP.

PART B - Biographical Information (To be completed by applicant)

Surname (last name)	Full given names (no initials) underline or circle name used
Surname at birth	All other names used (nicknames; former surnames)

Date of birth			Place of birth - City	Province/State	Country
Year	Month	Day			

Birth Certificate Number:	Province of Issue:

Sex Female ◯ Male ◯	Marital Status	Eye Colour	Hair Colour	Height (cm/in)	Weight (kg/lbs)

Municipality & Country of Birth	Port of Entry	Date of Entry

If Naturalized Canadian provide Certificate Number	Date of Issue
If Permanent Resident provide Certificate Number	Date of Issue
Have you ever been convicted in Canada of an offence for which you have not been granted a pardon? If yes, please provide more information.	☐ Yes ☐ No
Have you ever been convicted outside Canada of an offence for which you have not been granted a pardon? If yes, please provide more information.	☐ Yes ☐ No

PART C - Addresses of all locations where you have resided during the last five (5) years, starting with most current. There should be no gaps. (Rural addresses to include lot and Civic number)

Apt #	Street #	Street Name	Civic number (if applicable)	From Y M	To Y M
City	Province or state	Postal Code	Country	Telephone number ( )	
Apt #	Street #	Street Name	Civic number (if applicable)	From Y M	To Y M
City	Province or state	Postal Code	Country	Telephone number ( )	
Apt #	Street #	Street Name	Civic number (if applicable)	From Y M	To Y M
City	Province or state	Postal Code	Country	Telephone number ( )	
Apt #	Street #	Street Name	Civic number (if applicable)	From Y M	To Y M
City	Province or state	Postal Code	Country	Telephone number ( )	
Apt #	Street #	Street Name	Civic number (if applicable)	From Y M	To Y M
City	Province or state	Postal Code	Country	Telephone number ( )	

Part D – EMPLOYMENT HISTORY - Name & address of employers, schools where you have worked/attended during the last five (5) years starting with most current. Include times of unemployment if applicable (there should be no gaps).

Name of employer/educational institution – do not use initials	From		To	
	Y	M	Y	M
Address of Employer/educational institution (street number, name, city, province or state and country)				

Name of employer/educational institution – do not use initials	From		To	
	Y	M	Y	M
Address of Employer/educational institution (street number, name, city, province or state and country)				

Name of employer/educational institution – do not use initials	From		To	
	Y	M	Y	M
Address of Employer/educational institution (street number, name, city, province or state and country)				

Name of employer/educational institution – do not use initials	From		To	
	Y	M	Y	M
Address of Employer/educational institution (street number, name, city, province or state and country)				

Part E – Marital Status/Common-Law Partnership

Current Status

Married ◯ Common-Law Partnership ◯ Separated ◯ Widowed ◯ Divorced ◯ Single ◯

Current Spouse/Common-Law Partner: Surname, Given names	Maiden Name (if applicable)	Present citizenship of Current Spouse/Common-Law Partner / Nationality
Sex: Female ◯ Male ◯		

Date of marriage/common-law partnership			City, province/state, country of marriage/common-law partnership
Y	M	D	

City, province/state, country of birth of spouse or common-law partner		Y	M	D
	Date of birth			
If born in Canada Birth Certificate Number	If separated, widowed, or divorced specify date			
Province of Issue				
If born outside of Canada Port and Date of Entry				

If Naturalized Canadian provide certificate number	
Date of Issue	
Present address (apartment number, street number, street name, city, province/state and country)	
Name and address of employer – do not use initials	
Previous Spouse/Common-Law Partnership: Surname, Given name(s) (if within past 5 years)	Present citizenship of Previous Spouse/Former Common-Law Partnership
Maiden Name (if applicable)	
Sex: Female ◯ Male ◯	

Date of marriage/common-law partnership			City, province/state and country of marriage/common-law partnership
Y	M	D	
Date of divorce, separation, deceased			City, province/state and country of divorce, separation, death
Y	M	D	

City, province/state, country of birth (if known)	Date of birth	Y	M	D

Present address (apartment number, street number, street name, city, province/state and country – if known)

Part F - Travel outside Canada 90 days or over in the last five (5) years

Date of Travel			Destination	Purpose of Travel
Y	M	D		
Date of Travel			Destination	Purpose of Travel
Y	M	D		
Date of Travel			Destination	Purpose of Travel
Y	M	D		
Date of Travel			Destination	Purpose of Travel
Y	M	D		
Date of Travel			Destination	Purpose of Travel
Y	M	D		

Part G – Consent and Certification

Providing misleading or false information on this application may result in a refusal or cancellation of the security clearance.

For security clearance purposes, I consent to the disclosure by the Royal Canadian Mounted Police (RCMP) to other law enforcement agencies, , of any and all information provided by me in support of this application. Without limiting the generality of the foregoing, this includes information relating to my date of birth, education, residential history, employment history, and immigration and citizenship status in Canada. I also consent to the disclosure and use of my fingerprints and facial image for identification purposes during the course of the security clearance process

For security clearance purposes, I hereby authorize Health Canada to seek, verify, assess, collect, and retain for a period of two (2) years after the expiry date of the producer's licence, any and all information relevant to this application including any criminal records and any and all information contained in law enforcement files, including intelligence gathered for law enforcement purposes, and information with respect to my immigration and citizenship status, as well as any and all information that will facilitate the conduct of a security assessment. This includes non-conviction information, charges before the courts, findings of guilt or convictions and court orders registered in my name in the National Repository of Criminal Records and local records available to police services.
For security clearance purposes only, I consent to the release by other Canadian institutions or agencies to Health Canada, information relevant to this application for a security clearance to enable Health Canada to perform security screening assessments in order to determine whether a security clearance should be granted to me.

This consent is given solely for security clearance purposes. Unless cancelled in writing by me and notification is given in writing to Health Canada, this consent shall remain valid for conducting all the necessary verifications, specified checks, assessments and/or investigations, including any subsequent required verifications, if need be, as well as any requirements for updates.

I certify that all the information set out by me in this application for a security clearance, including any supporting documentation, is true and correct to the best of my knowledge and belief.

_____

Applicant Name Printed in Block Letters

_____ _____

Applicant's Signature Date (AAAA/MM/DD)

_____ _____

Home telephone Work telephone

IMPORTANT INFORMATION AND INSTRUCTIONS FOR COMPLETION OF SECURITY CLEARANCE FORM UNDER THE MARIHUANA FOR MEDICAL PURPOSES REGULATIONS (MMPR)

NOTE: As part of the Application to Become a Licensed Producer under the Marihuana for Medical Purposes Regulations, a Security Clearance Application Form must be completed by the applicant. A duly completed Security Clearance Application Form must be submitted for all parties identified in the Application to Become a Licensed Producer under the *Marihuana for Medical Purposes Regulations*. The applicants that apply as an individual include the proposed Senior Person in Charge, the proposed Responsible Person in Charge, any proposed Alternate Responsible Person(s) in Charge. In the case of a corporation, each Director and Officer of the corporation must also complete a security clearance form.

1. General:

1.1 If clarification of information is required, a Canadian Government Official may contact the applicant to obtain additional information in order to complete the security screening investigation and an interview of the applicant may be requested.

1.2 This form is to be completed using an automated system or printed in block letter format in black ink.

1.3 Please read and follow the instructions carefully.

1.4 The original signed copy must be submitted.

1.5 It is important that a copy of the completed application be retained by the applicant for future reference.

1.6 Incomplete or illegible forms will NOT be considered.

1.7 All names are to be in full (no initials).

1.8 Addresses are to include, where applicable, civic or township name and the lot and concession numbers.

1.9 If information is not known or is unavailable please indicate this on the form and on a separate sheet of paper explain the cause of circumstances.

1.10 All dates are to be entered in order of, YEAR, MONTH and DAY as applicable.

1.11 If space allotted in any portion of the form is insufficient please use a separate sheet of paper using the same format.

2. Part A: Requirements checklist

2.1 Application completed and signed. All required additional documentation to be submitted with application.

2.2 Health Canada to verify that all required documentation has been received.

3. Part B: Biographical Information

3.1 To be completed by the applicant.

3.2 If naturalized Canadian, it is important to show the certificate number and date of issue. Please include a copy of the certificate with the application form.

3.3 If permanent resident, it is important to show the certificate number and date of issue. Please include a copy of the certificate with the application form.

4. Part C: Address History

4.1 To be completed by applicant.

4.2 Ensure current address is recorded first.

4.3 Addresses must cover the last five (5) years from date of application and should contain no gaps.

4.4 The postal code is mandatory for the current address, and if known, for previous address.

4.5 For rural area, include civic number or lot, concession and township number.

5. Part D: Employment History

5.1 To be completed by applicant.

5.2 Ensure current employment is recorded first.

5.3 Employment history must cover the last five (5) years from date of application. Include periods of time at school or unemployment to ensure no gap in the five year period.

5.4 Full name and full address of employer/educational institution is required. No initials.

6. Part E: Marital Status/Common-law partnership

6.1 To be completed by applicant.

6.2 Common-law partnership in relation to the applicant, means a person who is cohabitating with the individual in a conjugal relationship, having so cohabitated for a period of at least one year. This includes persons of the same sex.

6.3 Include current spouse/common-law partner as applicable.

6.4 If any person is deceased, date of death and last address while living are to be shown.

6.5 Include previous spouse/common-law partner as applicable during the last five years. If a person is deceased, date of death.

6.6 All other questions to be answered as set forth.

7. Part F: Travel outside of Canada

7.1 To be completed by applicant.

7.2 Provide the dates, destination and purpose of any travel of 90 days or more outside of Canada during the five (5) years preceding the application. This excludes travel for government business.

8. Part G: Signature and Date

8.1 Application must be signed and dated by applicant.

Health Canada Santé Canada

***Canada Gazette*, Part II, publication of MMPR**

June 19, 2013

GUIDANCE DOCUMENT

Building and Production Security Requirements for Marihuana for Medical Purposes

Published by authority of the
Minister of Health

Controlled Substances and Tobacco Directorate
Healthy Environments and Consumer Safety Branch

Canada

Pub: 130083

Également disponible en français sous le titre: *Exigences en matière de sécurité des bâtiments et de la production de marihuana à des fins médicales.*

FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in the document, to allow the Department to adequately mitigate the risk of diversion of controlled substances to an illicit market or use.

This document should be read in conjunction with the relevant sections of other applicable guidance documents and the *Directive on Physical Security Requirements for Controlled Substances*.

TABLE OF CONTENTS

1. Purpose

The document is intended to help Licensed Producers (LPs) comply with Division 3 security measure requirements of the *Marihuana for Medical Purposes Regulations* (MMPR) which include general security measures, and security measures for the perimeter of site and areas within a site where cannabis is present.

LP's should note that this guidance document **does not** apply to the storage of dried marihuana, marihuana seeds and cannabis used solely for the purpose of testing in order to determine the percentages of cannabinoids in dried marihuana. The security measures for the storage of these substances can be found in Health Canada's *Directive on Physical Security Requirements for Controlled Substances* (Security Directive). The Security Directive establishes realistic minimum security standards for the **storage** of controlled substances and applies to dried marihuana, marihuana seeds, and to cannabis used solely for the purpose of conducting in-vitro testing in order to determine the percentages of cannabinoids in dried marihuana (both packaged and unpackaged). In addition to the requirements included in the Security Directive, there are specific outcome based requirements set out in Division 3 of the MMPR. These requirements aim to prevent unauthorized access to your site and to restrict and monitor access to areas within your site where cannabis is present.

It is the LP's responsibility to ensure that provincial, municipal and federal legislation including building and fire codes are complied with. Health Canada's Office of Controlled Substances is the authority responsible for licensing and compliance monitoring under the *Controlled Drugs and Substances Act* (CDSA) and MMPR.

2. Background

The safeguarding of controlled substances is an issue that confronts all manufacturers, distributors, practitioners, pharmacists, law enforcement and government. Health Canada limits the handling of these substances through policies, guidelines and legislation such as the CDSA, the *Narcotic Control Regulations* (NCR) and the MMPR. Cannabis, its preparations, derivatives, and similar synthetic preparations as listed under Schedule II of the CDSA are included in the definition of a controlled substance. Those wishing to engage in lawful activities must, therefore, be properly licensed and ensure that the controlled substances are adequately secured and safeguarded at all times for public safety and to minimize risks of diversion.

3. Scope

This guidance document is applicable if you are interested in producing marihuana for medical purposes or want to engage in any other regulated activity set out in the MMPR. These guidelines outline regulatory requirements and include examples of security measures that you can put in place for both building construction and electronic systems. The Procedures section of this document will assist you on how to meet these requirements. Furthermore, it is the LP's responsibility to ensure that provincial, municipal and federal legislation including building and fire codes are complied with.

This guidance document does not apply to licensed dealers under the *Narcotic Control Regulations*, the *Benzodiazepines and Other Targeted Substances Regulations*, and Part G or Part J of the *Food and Drug Regulations*.

Please note that all waste cannabis material from cultivation or production is considered to be a controlled substance with the exception of mature cannabis stalks that do not include leaves, flowers, branches or seeds; and fibers derived from the stalks as well as any non-viable cannabis seeds as per Schedule II of the CDSA. Waste cannabis material that is a controlled substance must be secured in accordance with the CDSA and as outlined in Health Canada's *Directive on Physical Security Requirements for Controlled Substances* (Security Directive) until destroyed.

4. Procedures

As part of the application to become a LP, you must provide a detailed description of the security measures at the proposed site, in accordance with Division 3 of the MMPR and the Security Directive, published by Health Canada, as amended from time to time. It is up to you to determine potential security risks at your site and to design and implement appropriate security systems and protocols to meet the regulatory requirements outlined above. Health Canada officials will review your security proposal as part of their consideration of your application. It is important that you seek appropriate professional advice before undertaking any construction work.

The security of your site and of the areas within your site where cannabis is present does not end with the design and construction. Security requirements detailed in the regulations require your attention on a continual basis. It is the ongoing responsibility of the LP to ensure that all requirements for securing their site, areas within their site where cannabis is present and the storage of cannabis and any activities relating to the production of marihuana for medical purposes (as per their licence) are met.

In addition, it is the responsibility of the LP to ensure that provincial, municipal and federal legislation including building and fire codes are complied with.

5. Specific Regulatory Provisions in Division 3 of the MMPR

In this section, specific regulatory provisions from the MMPR are reproduced in bold and italicized text, followed by guidance on how these regulatory provisions can be met.

5.1 Regulatory Provisions Relating to Securing Your Site

MMPR s41	***A licensed producer must ensure that the security measures set out in Division 3 are carried out.***
MMPR s42	***The licensed producer's site must be designed in a manner that prevents unauthorized access.***
MMPR s47	***Those areas [within a site where cannabis is present] must include physical barriers that prevent unauthorized access.***

Guidance: Signage and Physical Barriers

If your site is a stand-alone building, or a space within a building that shares walls, then physical barriers and signage posted at the perimeter and entrance to your building/space can assist in ensuring that your site is secure. The main purpose is to prevent unauthorized access and to act as a definite demarcation. Physical barriers are required for securing all areas within a site where cannabis is present. Physical barriers should provide sufficient resistance to impede unauthorized access to the premises where cannabis is present.

For example, a physical barrier of some kind (e.g. a fence surrounding the site) and a sign stating that it is private property or a restricted area and that unauthorized access is prohibited are appropriate.

Guidance: Entrances, Doors and Frames

Minimizing the number of entranceways to the site and areas within a site where cannabis is present will assist in securing and monitoring the space; however, it should remain consistent with fire and building safety codes. Securing all entrances to the building, site or areas within a site where cannabis is present would prevent unauthorized access.

For example, entranceways to areas within a site where cannabis is present could be equipped with commercial steel doors and frames. Doors may be specified as fire rated where required. The doors could also be equipped with the appropriate locking hardware, door closers, contact switches, and electronic access control mechanisms, to assist in providing appropriate security against unauthorized access.

Keeping your entranceways closed and locked to the extent possible given your business operations can assist in ensuring that your site and areas within a site where cannabis is present are secure.

Keeping doors and entrances to the areas within your site where cannabis is present closed at all times with an operational intrusion detection system on (alarm system that operates at all times) would further prevent unauthorized access.

Guidance: Openings, Ducts and Mechanical/Electrical Pass-Throughs

Minimizing the number of openings, ducts and pass-throughs in your site and areas within your site where cannabis is present will assist in preventing unauthorized access.

Protecting all other openings with security screens, steel bars or equivalent material, welded to steel frames will assist in preventing unauthorized access to your site. The screens and bars are most effective in preventing unauthorized access including quick entry, grab and exit type intrusions.

Where appropriate to accommodate pipe or conduit movement or expansion, pipes and conduits can be enclosed in a close-fitting sheet metal sleeve and fastened to a frame to provide appropriate security.

Guidance: Wall Construction

The walls of your site should be constructed to assist in ensuring that unauthorized access to your site and areas within your site where cannabis is present is prevented.

For example, slab-to-slab construction and steel mesh sheets attached to the underside of structural joists can assist in ensuring wall security.

Guidance: Glazing Panel Security

Appropriate use of glazing panels can assist in ensuring that unauthorized access to your site is prevented.

For example, any glazing panels used in roofing (in a greenhouse for example) should be attached directly to the roof structure in such a manner as to preventing removal from the outside.

Building security can be further ensured by using appropriate electronic equipment to monitor glazing elements, including sensors that can detect breakage of glazing panels.

Mechanisms that can provide secure monitoring of glazing elements include at least one of the following:

- Glass-break sensors of sufficient number may be appropriately installed to provide 100% coverage of the glazing area.
- Electrically conductive foil or wire can be incorporated in the glazing elements to provide detection of breaks.
- Volumetric or beam-break detection systems can be employed to provide 100% coverage of the interior surface area of the glazing.

5.2 Regulatory Provisions Relating to Monitoring and Detection

Perimeter of the Site

MMPR s43. (1)	***The perimeter of the licensed producer's site must be visually monitored at all times by visual recording devices to detect any attempted or actual unauthorized access.***
MMPR s43. (2)	***The [visual recording] devices must, in the conditions under which they are used, be capable of recording in a visible manner any attempted or actual unauthorized access.***
MMPR s44.	***The perimeter of the licenced producer's site must be secured by an intrusion detection system that operates at all times and that allows for the detection of any attempted or actual unauthorized access to or movement in the site or tampering with the system.***
MMPR s45.(1)	***The system must be monitored at all times by personnel who must determine the appropriate steps to be taken in response to the detection of any occurrence [of attempted or actual unauthorized access].***
MMPR s45.(2)	***If any such occurrence is detected, the personnel must make a record of: the date, time of the occurrence; and the***

measures taken in response to it and the date and time when they were taken.

Areas Within a Site Where Cannabis is Present

MMPR s48.(1) ***Those areas [within a site where cannabis is present] must be visually monitored at all times by visual recording devices to detect illicit conduct.***

MMPR s48.(2) ***The devices must, in the conditions under which they are used, be capable of recording in a visible manner illicit conduct.***

MMPR s51.(1) ***The intrusion detection system must be monitored at all times by personnel who must determine the appropriate steps to be taken in response to the detection of any occurrence [of illicit conduct, any attempted or actual unauthorized access to or movement in those areas or tampering with the system].***

MMPR s51.(2) ***If any such occurrence is detected, the personnel must make a record of: the date, time of the occurrence; and the measures taken in response to it and the date and time when they were taken.***

Guidance: Video Coverage

Visual monitoring of the perimeter of your site, as well as the areas areas within your site where cannabis is present can be achieved using closed circuit video equipment (CCVE). Appropriate lighting equipment in conjunction with CCVE can assist in the detection, classification, assessment, and recognition of the images recorded.

Camera should be in sufficient number and appropriately located to cover the area to be monitored.

Guidance: Redundancy and Back-Ups

Keeping all cameras recording 24/7, and having appropriate back-up mechanisms in place can achieve the appropriate coverage to detect illegal activity, unauthorized access and any attempts to breach the security of your site and of the areas within your site where cannabis is present.

Back-up mechanisms must ensure that all visual recordings and records of a detected occurrence be retained for two years. These back-up mechanisms may include storing the visual recordings on multiple media devices.

5.3 Regulatory Provisions Relating to Access Control

MMPR s42.	***The licensed producer's site must be designed in a manner that prevents unauthorized access.***
MMPR s46. (1)	***Access to each area within a site where cannabis is present must be restricted to persons whose presence in the area is required by their work responsibilities.***
MMPRP s46.(2)	***The responsible person in charge or, if applicable, the alternate responsible person in charge must be physically present while other persons are in those areas.***
MMPR s46.(3)	***A record must be made of the identity of every person entering or exiting those areas.***

Guidance: Securing access to the site perimeter and areas within a site where cannabis is present

There is a wide range of appropriate electronic access control systems, including intrusion detection mechanisms and CCVE that may be employed to ensure that access to the site, and areas within the site where cannabis is present, is restricted to the appropriate personnel and that a record is kept of each person entering or exiting those areas.

The system that you install must be capable of identifying each individual who enters or leaves restricted areas to comply with regulatory requirements. A personal identification number (PIN) credential system alone is not sufficient for access control because PINs can be purposefully or inadvertently disclosed.

For example, a security system that requires a PIN and an identification card, or biometrics and visual monitoring are examples of ways to prevent both unauthorized access to those areas within a site where cannabis is present, and keep track of the movements of personnel that enter and leave those areas.

Guidance: Security System Control Mechanisms

Steps should be taken to ensure the appropriate control of codes, keys, combinations and other elements of your security system.

For example, to ensure appropriate security, only senior personnel including the senior person in charge, the responsible person in charge and any alternate responsible persons in charge should have access to alarm codes, vault combinations and other security elements for the site. Changing combinations and codes on a regular basis and when there are any changes with any senior personnel will assist in ensuring appropriate control of the security system.

5.4 Regulatory Provisions Relating to Intrusion Detection

Perimeter of the Site

MMPR s44.	***The perimeter of the licenced producer's site must be secured by an intrusion detection system that operates at all times and that allows for the detection of any attempted or actual unauthorized access to or movement in the site or tampering with the system.***
MMPR s45.(1)	***The system must be monitored at all times by personnel who must determine the appropriate steps to be taken in response to any occurrence of an attempted or actual unauthorized access to or movement in the site or tampering with the system.***
MMPR s45.(2)	***If any such occurrence is detected, the personnel must make a record of: the date, time of the occurrence as well as all measures taken in response to it and the date and time when they were taken.***

Areas within a site where cannabis is present

MMPR s49.	***Those areas [within a site where cannabis is present] must be secured by an intrusion detection system that operates at all times and that allows for the detection of any attempted or actual unauthorized access to or movement in those areas or tampering with the system.***
MMPR s51.	***The intrusion detection system must be monitored at all times by personnel who must determine the appropriate steps to be taken in response to the detection of any occurrence [of illicit conduct, any attempted or actual unauthorized access to or movement in those areas or tampering with the system].***

A robust intrusion detection system can assist in securing both your site and areas within your site where cannabis is present.

Guidance: Monitoring

Monitoring your site's perimeter and areas within your site where cannabis is present via an intrusion detection system with personnel in a central location will

allow your personnel to detect any unauthorized attempts to enter those areas; or to tamper with security equipment. Appropriately trained personnel will assist in responding to any incident involving detected unauthorized activity.

When there are no responsible personnel present, a link to a monitoring station will enable notification to the appropriate personnel and law enforcement.

A response plan should be designed to ensure quick action when detection has occurred.

Guidance: Records of Detected Matters

Keeping all cameras recording 24/7, and having appropriate back-up mechanisms in place can achieve the appropriate coverage to detect illegal activity, unauthorized access and any attempts to breach the security of your site and areas within your site where cannabis is present.

Back-up mechanisms must ensure that all visual recordings and records of a detected occurrence be retained for two years. These back-up mechanisms may include storing the visual recordings on multiple media devices.

Guidance: Tampering

The effectiveness of any system is dependent on the signal reaching the individuals responsible for the monitoring of the signal and the response to its warning. Depending on how the signal is carried, tampering with the line carrying the signal may result in the signal not reaching its intended destination. An acceptable system should be able to identify, record, and notify if the lines are tampered with or if an attempt has been made.

A response plan should be designed to ensure quick action when tampering occurs.

Guidance: Power Supply

In order to comply with regulations, your security system must include visual recording devices, access control and an intrusion detection system which must operate on a continuous basis.

For example, supporting your security system and all components (e.g., sensors, control units and communicators/enunciators, volumetric sensors, glass-break detectors, beam-break sensors) with an uninterruptible power supply sufficient for 24/7 continuous operation would effectively maintain the integrity of your security system.

5.5 Regulatory Provision Relating to Air Filtration

MMPR s50. ***Those areas [within a site where cannabis is present] must be equipped with a system that filters air to prevent the escape of odours and, if present, pollen.***

Guidance: Air Filtration

To assist in the prevention of the escape of pollen, odours, and other particles, all exhaust air from your cultivation area and other areas within your site where cannabis is present can be filtered through appropriate air filtration systems.

For example, a high-efficiency particle air filter such as a H13 HEPA filter can ensure appropriate ventilation and filtration of exhaust air.

This is **Exhibit " C "** referred to in the
Affidavit of **TODD CAIN**
Affirmed before me
at the City of Ottawa,
in the Province of Ontario,
this 7th day of February 2014.

A Notary Public in for the Province of Ontario

DEPARTMENT OF FISHERIES AND OCEANS

FISHERIES ACT

Notice of intent with respect to amending the Pacific Aquaculture Regulations *to include Aquaculture Licence Fees*

Fisheries and Oceans Canada intends to charge licence fees for all federally licensed aquaculture operations in British Columbia, with the exception of non-commercial production facilities including not-for-profit, salmon enhancement, and universities. The licence fee will be implemented through an amendment to the *Pacific Aquaculture Regulations*. This process is also subject to the provisions of the *User Fees Act*, which requires that the fee proposal be tabled in Parliament before it is finalized.

A discussion paper summarizing the proposed fee structure, service standards, consultations to date, and the anticipated impacts of the proposal will be posted on the Department's Web site. All affected and interested parties are invited to review the discussion paper, and participate fully during the comment period of the consultation process which will begin on December 17, 2012, and conclude on January 16, 2013.

For further information, please consult the Department's Web site at www.dfo-mpo.gc.ca/aquaculture/aquaculture-eng.htm.

December 15, 2012

AQUACULTURE MANAGEMENT DIRECTORATE

[50-1-o]

MINISTÈRE DES PÊCHES ET DES OCÉANS

LOI SUR LES PÊCHES

Avis d'intention concernant la modification du Règlement du Pacifique sur l'aquaculture *afin d'y ajouter les droits de permis d'aquaculture*

Pêches et Océans Canada a l'intention d'imposer des droits de permis à toutes les activités d'aquaculture réglementées par le gouvernement fédéral en Colombie-Britannique, sauf dans le cas des installations de production non commerciales telles que les établissements à but non lucratif, les organismes de mise en valeur du saumon et les universités. Les droits de permis seront officialisés par l'entremise de la modification du *Règlement du Pacifique sur l'aquaculture*. Cette mesure est assujettie aux dispositions de la *Loi sur les frais d'utilisation*, qui exigent le dépôt au Parlement des droits proposés avant d'être finalisée.

Un document de travail résumant le barème de droits proposé, les normes de service, les activités de consultation menées jusqu'à présent et les incidences prévues de la mesure sera également affiché sur le site Web du Ministère. On invite toutes les parties intéressées à examiner le document de travail et à s'exprimer librement pendant la période des commentaires du processus de consultation qui se déroulera du 17 décembre 2012 au 16 janvier 2013.

Pour de plus amples renseignements, veuillez consulter le site Web du Ministère au www.dfo-mpo.gc.ca/aquaculture/aquaculture-fra.htm.

Le 15 décembre 2012

LA DIRECTION GÉNÉRALE DE LA GESTION DE L'AQUACULTURE

[50-1-o]

DEPARTMENT OF HEALTH

CONTROLLED DRUGS AND SUBSTANCES ACT

Notice to interested parties — Proposed improvements to the Marihuana Medical Access Program (MMAP) — Research and development activities

On December 15, 2012, Health Canada is publishing the proposed *Marihuana for Medical Purposes Regulations* (MMPR) in the *Canada Gazette*, Part I. The proposed Regulations can be found at www.gazette.gc.ca/rp-pr/p1/2012/2012-12-15/html/reg4-eng.html.

The proposed Regulations would establish the conditions for a competitive industry of licensed producers, which would offer individuals access to dried marihuana for medical purposes, produced under secure and sanitary conditions. A licensed producer (LP) would have to meet regulatory requirements for elements such as quality control standards and security measures. This would reduce risks to public health, safety and security resulting from such production. After the new Regulations come into force, interested persons would be able to apply for a licence and, if they qualify, immediately begin producing and distributing dried marihuana for medical purposes.

Parties who are considering becoming an LP and are interested in engaging in certain research and development activities such as testing marihuana or testing growing conditions on-site may do so prior to the MMPR coming into force using existing mechanisms

MINISTÈRE DE LA SANTÉ

LOI RÉGLEMENTANT CERTAINES DROGUES ET AUTRES SUBSTANCES

Avis aux parties intéressées — Améliorations proposées aux activités de recherche et de développement du Programme d'accès à la marihuana à des fins médicales (PAMFM)

Le 15 décembre 2012, Santé Canada publie le *Règlement sur l'accès à la marihuana à des fins médicales* (RAMFM) proposé dans la Partie I de la *Gazette du Canada*. Le projet de règlement se trouve au www.gazette.gc.ca/rp-pr/p1/2012/2012-12-15/html/reg4-fra.html.

Le projet de règlement établit les conditions pour une industrie concurrentielle de producteurs autorisés, ce qui permettrait aux individus d'obtenir de la marihuana séchée à des fins médicales produite dans des conditions sanitaires et sécuritaires. Les producteurs autorisés devront respecter les exigences réglementaires liées à des éléments comme les normes relatives au contrôle de la qualité et les mesures de sécurité. Cela réduirait les risques pour la santé et la sécurité de la population que constitue une telle production. Une fois le nouveau règlement entré en vigueur, les personnes intéressées pourront présenter une demande de licence et si elles sont admissibles, commencer immédiatement à produire et à distribuer de la marihuana séchée à des fins médicales.

Les parties qui envisagent devenir producteur autorisé et qui sont intéressées à prendre part à certaines activités de recherche et de développement, comme l'évaluation de la marihuana ou l'évaluation des conditions de culture sur place, peuvent le faire

under the *Controlled Drugs and Substances Act* (CDSA) and the *Narcotic Control Regulations* (NCR).

These mechanisms include

1. a licence issued under section 9 of the NCR (licensed dealer) which would enable activities such as possession to test marihuana plant material;
2. a licence to cultivate, gather or produce marihuana for scientific purposes issued in accordance with section 67 of the NCR; and/or
3. an exemption issued under section 56 of the CDSA for other activities with marihuana such as testing packaging methods and materials.

Information and documents that would be considered in an application include but are not limited to

- a statement indicating that these research and development activities are being conducted with the intent of eventually applying to become a licensed producer;
- a declaration from the applicant that the municipality, local law enforcement, and local fire officials where the proposed activities are to be conducted have been notified of the proposed research and development activities with marihuana;
- valid criminal record checks of the person responsible for the licence or exemption, the person in charge of the research project, if applicable, and the person in charge of production, indicating that they have not been convicted, as an adult, within the preceding 10 years, of a designated drug offence or a designated criminal offence as these terms are defined in the NCR;
- a letter from the owner of the proposed location where the proposed activities are to be conducted indicating that there is no objection to its use for marihuana production if the location is not owned by the applicant; and
- appropriate security measures, in accordance with the requirements of the *Directive on Physical Security Requirements for Controlled Substances* found at www.hc-sc.gc.ca/hc-ps/pubs/precurs/dealers-distrib/phys_securit_directive/index-eng.php and the guidance document *Building and Production Security Requirements for Marihuana for Medical Purposes* found at www.hc-sc.gc.ca/dhp-mps/marihuana/future-avenir/securit-eng.php.

In deciding whether to issue a licence or exemption, the Minister would review applications on a case-by-case basis and may consider other factors such as the risk to public health, safety or security. This would include the risk of marihuana being diverted to an illicit market or an illicit use.

It is also worth noting that if the proposed MMPR are promulgated, the issuance of a licence or exemption to conduct research and development activities does not guarantee the issuance of a licence under the proposed new Regulations. Producer licences can only be issued once the new Regulations come into force.

Interested parties wishing to conduct research and development activities may initiate this process by providing Health Canada with a letter expressing their interest and providing the

avant l'entrée en vigueur du RAMFM en se servant des mécanismes déjà prévus par la *Loi réglementant certaines drogues et autres substances* (LRCDAS) et le *Règlement sur les stupéfiants* (RS).

Les mécanismes comprennent :

1. une licence délivrée en vertu de l'article 9 du RS (distributeur autorisé) qui autoriserait des activités comme la possession pour évaluer les plants de marihuana;
2. une licence pour cultiver, récolter ou produire de la marihuana à des fins scientifiques délivrée en conformité avec l'article 67 du RS;
3. une exemption délivrée en vertu de l'article 56 de la LRCDAS pour d'autres activités liées à la marihuana, comme l'évaluation des méthodes et du matériel d'emballage.

Voici certains renseignements et documents qui seraient pris en compte dans une demande :

- un énoncé indiquant que ces activités de recherche et de développement sont menées dans le but éventuel de faire une demande pour devenir producteur autorisé;
- une déclaration du demandeur selon laquelle la municipalité, les représentants locaux de la loi et des services d'incendie où les activités proposées doivent avoir lieu ont été avisés des activités de recherche et de développement proposées avec la marihuana;
- les vérifications valides du casier judiciaire de la personne responsable de la licence ou de l'exemption, de la personne chargée du projet de recherche, s'il y a lieu, et de la personne chargée de la production, casier judiciaire où il est indiqué qu'elle n'a pas été condamnée, comme adulte, au cours des 10 dernières années, pour une infraction désignée en matière de drogue ou une infraction criminelle désignée, conformément à la définition de ces termes dans le RS;
- une lettre du propriétaire du lieu proposé où les activités proposées doivent avoir lieu et dans laquelle il est indiqué qu'il n'y a aucune objection quant à l'utilisation du lieu pour la production de marihuana si le lieu n'est pas la propriété du demandeur;
- les mesures de sécurité appropriées, en conformité avec les exigences de la *Directive sur les exigences en matière de sécurité physique pour les substances désignées* se trouvant à l'adresse suivante : www.hc-sc.gc.ca/hc-ps/pubs/precurs/dealers-distrib/phys_securit_directive/index-fra.php et du document d'orientation *Exigences en matière de sécurité des bâtiments et de la production de marihuana à des fins médicales* se trouvant à l'adresse suivante : www.hc-sc.gc.ca/dhp-mps/marihuana/future-avenir/securit-fra.php.

Dans le cadre de sa décision d'émettre une licence ou une exemption, le ministre examinera les demandes au cas par cas et pourrait tenir compte de facteurs comme le risque pour la santé ou la sécurité de la population, y compris le risque que la marihuana soit détournée vers un marché illicite ou que cette marihuana soit utilisée à des fins illicites.

De plus, veuillez prendre note que si le RAMFM est promulgué, l'émission d'une licence ou d'une exemption concernant le déroulement d'activités de recherche ou de développement ne garantit pas l'émission d'une licence en vertu du nouveau règlement proposé. Les licences de producteur ne peuvent être émises que lorsque la nouvelle réglementation sera en vigueur.

Les parties intéressées désireuses de mener des activités de recherche et de développement peuvent amorcer ce processus en faisant parvenir à Santé Canada une lettre dans laquelle elles

information indicated in the first four points listed above, as applicable, at the following address:

Office of Controlled Substances
Controlled Substances and Tobacco Directorate
Healthy Environments and Consumer Safety Branch
Health Canada, AL: 3503A
Ottawa, Ontario
K1A 1B9

Please note that if interested parties wish to conduct activities in addition to research and development, such as producing marihuana for the purposes of sale before the proposed MMPR are in force, those parties must comply with the applicable requirements of the *Food and Drugs Act* and the *Food and Drug Regulations* (e.g. requirements for clinical trials which demonstrate clinical efficacy and safety).

For those requiring more information regarding the application process or information regarding the availability of a legal supply of seeds or marihuana for research and development activities, please contact the Office of Controlled Substances at OCS-BSC@hc-sc.gc.ca.

[50-1-o]

manifestent leur intérêt et en communiquant l'information indiquée dans les quatre premiers points énumérés précédemment, s'il y a lieu, à l'adresse suivante :

Bureau des substances contrôlées
Direction des substances contrôlées et de la lutte au tabagisme
Direction générale de la santé environnementale et de la sécurité des consommateurs
Santé Canada, Indice de l'adresse : 3503A
Ottawa (Ontario)
K1A 1B9

Veuillez prendre note que si les parties intéressées souhaitent mener des activités en plus de la recherche et du développement, comme la production de marihuana pour la vente avant l'entrée en vigueur du RAMFM, ces parties doivent se conformer aux exigences applicables de la *Loi sur les aliments et drogues* et du *Règlement sur les aliments et drogues* (par exemple aux exigences de mener des essais cliniques sur l'efficacité et l'innocuité).

Les personnes désireuses d'obtenir de plus amples renseignements sur le processus de demande ou de l'information sur la disponibilité d'un approvisionnement légal en graines ou en marihuana pour des activités de recherche et de développement peuvent envoyer un courriel au Bureau des substances contrôlées à l'adresse suivante : OCS-BSC@hc-sc.gc.ca.

[50-1-o]

DEPARTMENT OF INDUSTRY

OFFICE OF THE REGISTRAR GENERAL

Appointments

Name and position/Nom et poste	*Order in Council/Décret*
Dedimus potestatem	
Commissioners to administer oaths/Commissaires à l'assermentation	
Within Canada/à l'intérieur du Canada	
Bocock, The Hon./L'hon. Randall S.	2012-1607
Gagné, The Hon./L'hon. Jocelyne	2012-1607
Gleason, The Hon./L'hon. Mary J. L.	2012-1607
Kane, The Hon./L'hon. Catherine M.	2012-1607
Within Alberta/à l'intérieur de l'Alberta	
Jones, The Hon./L'hon. Craig M.	2012-1607
Millar, The Hon./L'hon. Bruce A.	2012-1607
Within British Columbia/à l'intérieur de la Colombie-Britannique	
Abrioux, The Hon./L'hon. Patrice	2012-1607
Fitch, The Hon./L'hon. Gregory J.	2012-1607
Jenkins, The Hon./L'hon. Robert W.	2012-1607
Tindale, The Hon./L'hon. Ronald S.	2012-1607
Weatherill, The Hon./L'hon. Gordon C.	2012-1607
Within Manitoba/à l'intérieur du Manitoba	
Rempel, The Hon./L'hon. Herbert	2012-1607
Within New Brunswick/à l'intérieur du Nouveau-Brunswick	
DeWare, The Hon./L'hon. Tracey K.	2012-1607
Within Newfoundland and Labrador/à l'intérieur de Terre-Neuve-et-Labrador	
McGrath, The Hon./L'hon. Rosalie	2012-1607
Within Northwest Territories/à l'intérieur des Territoires du Nord-Ouest	
Shaner, The Hon./L'hon. Karan M.	2012-1607
Smallwood, The Hon./L'hon. Shannon	2012-1607
Within Nova Scotia/à l'intérieur de la Nouvelle-Écosse	
Wood, The Hon./L'hon. Michael J.	2012-1607

MINISTÈRE DE L'INDUSTRIE

BUREAU DU REGISTRAIRE GÉNÉRAL

Nominations

Name and position/Nom et poste	*Order in Council/Décret*
Dedimus potestatem	
Commissioners to administer oaths/Commissaires à l'assermentation	
Within Canada/à l'intérieur du Canada	
Bocock, The Hon./L'hon. Randall S.	2012-1607
Gagné, The Hon./L'hon. Jocelyne	2012-1607
Gleason, The Hon./L'hon. Mary J. L.	2012-1607
Kane, The Hon./L'hon. Catherine M.	2012-1607
Within Alberta/à l'intérieur de l'Alberta	
Jones, The Hon./L'hon. Craig M.	2012-1607
Millar, The Hon./L'hon. Bruce A.	2012-1607
Within British Columbia/à l'intérieur de la Colombie-Britannique	
Abrioux, The Hon./L'hon. Patrice	2012-1607
Fitch, The Hon./L'hon. Gregory J.	2012-1607
Jenkins, The Hon./L'hon. Robert W.	2012-1607
Tindale, The Hon./L'hon. Ronald S.	2012-1607
Weatherill, The Hon./L'hon. Gordon C.	2012-1607
Within Manitoba/à l'intérieur du Manitoba	
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Within New Brunswick/à l'intérieur du Nouveau-Brunswick	
DeWare, The Hon./L'hon. Tracey K.	2012-1607
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Within Northwest Territories/à l'intérieur des Territoires du Nord-Ouest	
Shaner, The Hon./L'hon. Karan M.	2012-1607
Smallwood, The Hon./L'hon. Shannon	2012-1607
Within Nova Scotia/à l'intérieur de la Nouvelle-Écosse	
Wood, The Hon./L'hon. Michael J.	2012-1607

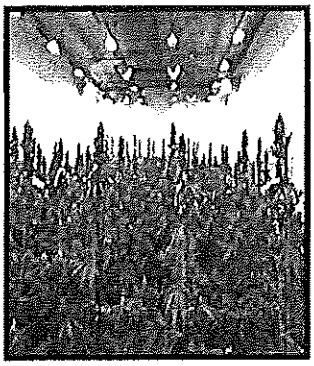
This is **Exhibit " D "** referred to in the
Affidavit of **TODD CAIN**
Affirmed before me
at the City of Ottawa,
in the Province of Ontario,
this 7th day of February 2014.

A Notary Public in for the Province of Ontario

bedrocan® canada

Varieties

Bedrocan Canada Offers 5 Varieties of Cannabis:



- Bedrocan – 22% THC
- Bedropuur – 24% THC
- Bedica – 14% THC
- Bediol – 6.5% THC & 8% CBD
- Bedrolite – <0.5% THC & 9% CBD

Bedrocan Canada is offering these 5 varieties of Cannabis for sale to Canadian patients at a flat rate of $7.50 per gram (includes shipping – some conditions apply). Each variety has a distinct level of cannabinoids (THC and CBD) guaranteed to be the same in every batch. Bedrocan's method of standardizing the chemical content of whole cannabis flowers is unique in the world. We also have a number of additional varieties that are ready for patient use or in some stage of standardization.

What are THC, CBD, and CBN?

Click on the tabs below to learn more about each variety.

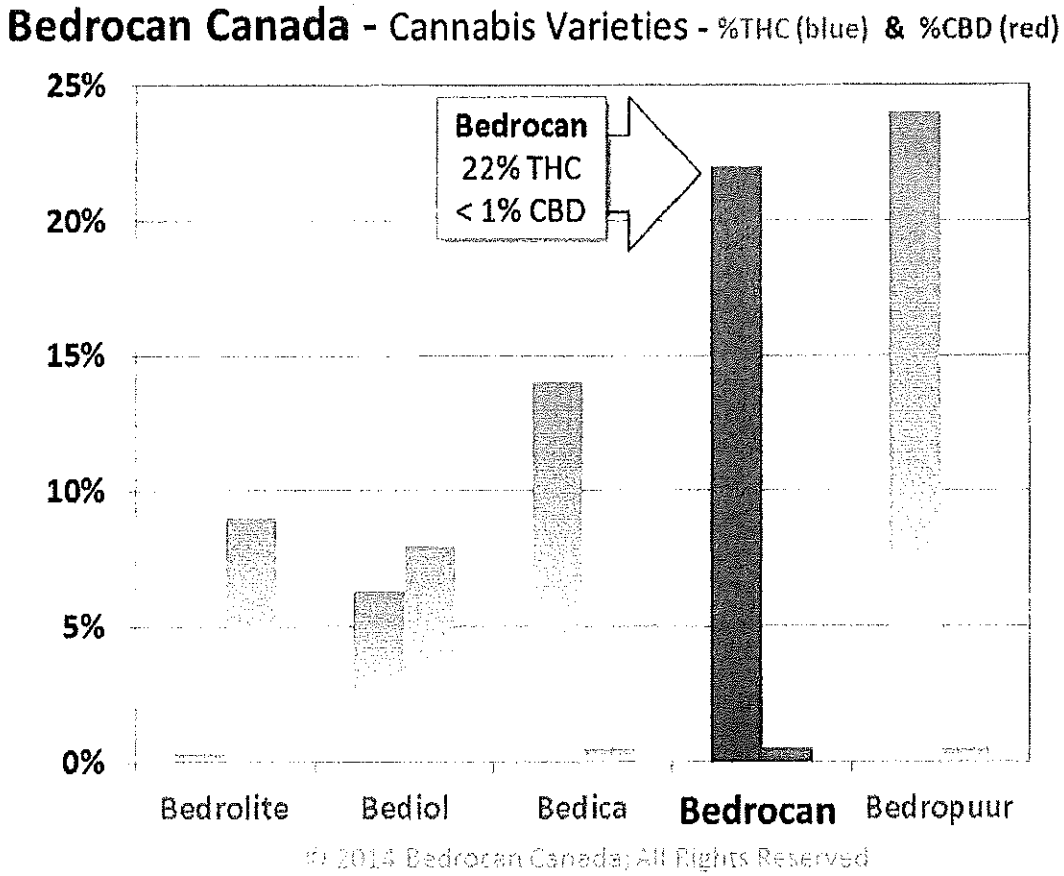
BEDROCAN® THC: 22 BEDROPUUR® THC: 24 BEDICA® THC: 14

BEDIOL® THC 6.5; CBD 8 BEDROLITE® CBD: 9 NEW VARIETIES

Bedrocan®

Content: 22% THC; CBD < 1%

Description: Bedrocan was developed in the Netherlands out of a requirement by the Dutch Health Ministry to have at least one "high THC" variety available to patients. It's a "sativa" plant type, bred because of its high yield, optimal growth characteristics, and derived from the popularly known "Jack Herer" cannabis variety. In order to appeal to existing use patterns and encourage patients to enter the official program in the Netherlands, care was taken to choose a variety that was already popularly used.



Published research with Bedrocan

Bedrocan supports the development of scientific research on medicinal cannabis.
The Bedrocan variety of cannabis was featured in the following published academic research articles.

1. Hazekamp, 2004. "Quantitative Analysis of Cannabinoids from Cannabis sativa Using 1H-NMR" Chem. Pharm. Bull. 52(6) 718—721.

2. Hazekamp, 2006. "An evaluation of the quality of medicinal grade cannabis in the Netherlands," Cannabinoids 2006;1(1):1-9.

3. Hazekamp, 2006. "Evaluation of a Vaporizing Device (Volcano1) for the Pulmonary Administration of Tetrahydrocannabinol," J. Pharm. Sci. 95(6); 1308-1317.

4. Hazekamp, 2007. "Cannabis tea revisited: A systematic evaluation of the cannabinoid composition of cannabis tea," Journal of Ethnopharmacology 113, 85–90.

5. de Jong, 2007. "Medicinal Cannabis Does Not Influence the Clinical Pharmacokinetics of Irinotecan and Docetaxel," The Oncologist 12:291–300.

6. Pomahacova, 2007. "Cannabis smoke condensate III: The cannabinoid content of vaporised Cannabis sativa," Inhalation Toxicology 21(13): 1108–1112.

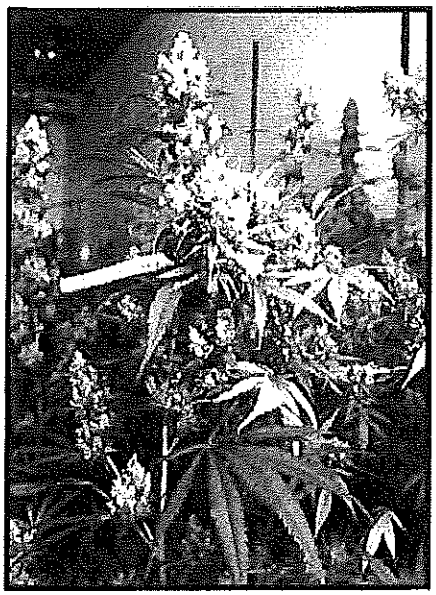
7. Fischedick, 2009. "A Qualitative and Quantitative HPTLC Densitometry Method for the Analysis of Cannabinoids in Cannabis sativa L.," Phytochem. Anal. 20, 421–426.

8. Fischedick, 2010. "Metabolic fingerprinting of Cannabis sativa L., cannabinoids and terpenoids for chemotaxonomic and drug standardization purposes Phytochemistry," 71(17-18): 2058-2073.

9. Fischedick, 2010. "Cannabinoid Receptor 1 Binding Activity and Quantitative Analysis of Cannabis sativa L. Smoke and Vapor," Chem. Pharm. Bull. 58(2) 201—207.

10. Hazekamp and Fischedick, 2012. "Cannabis – from cultivar to chemovar," Drug Testing and Analysis 4: 660-667.

Bedrocan's varieties of medicinal cannabis are produced to pharmaceutical standards and are free of chemical and microbiological contaminants in accordance with Health Canada standards, which include strict quality assurance procedures, as well as regular testing for contaminants such as mold, fungus, bacteria, and heavy metals, which may pose a serious risk to patients with compromised immune systems. Bedrocan uses absolutely no chemical pesticides.



Careers

Canada Medicinal Cannabis

bedrocan® canada

Frequently Asked Questions

Here are some frequently asked questions about Bedrocan, about the MMPR, and about cannabis for medical use. If the information you're looking for isn't here, **contact us** and we'll track it down for you.

On Medicinal Cannabis

WHERE CAN I GO TO READ ABOUT THE SCIENCE OF CANNABIS FOR MEDICAL USE?

There are a number of great resources out there. In addition to what you'll find right here, we recommend the International Association of Cannabinoid Medicines (IACM), the Canadian Consortium for the Investigation of Cannabinoids (CCIC), the International Cannabinoid Research Society, and Health Canada's Information for Health Care Professionals.

IF CANNABIS IS A MEDICINE, WHY CAN'T I GET IT IN A PHARAMCY?

To be called a "medicine" and sold in pharmacies in Canada, prescription drugs have to be evaluated by Health Canada. Typically, Health Canada would review 3 phases of clinical studies conducted by a drug company to look at a drug's safety and efficacy. This hasn't happened yet for cannabis (although Bedrocan has begun these studies).

The new Marihuana for Medical Purposes Regulations (MMPR) do allow for distribution in pharmacies, but only if approved at the provincial level.

IF THERE'S SO MUCH RESEARCH, WHY ISN'T CANNABIS APPROVED AS A MEDICINE?

In order to be approved as drug, Health Canada must evaluate 3 phases of clinical studies showing safety and targeting a specific illness. While cannabis is perhaps the most researched plant in the world, there have never been the specific types of studies done within this process, with the goal of actually "approving" cannabis.

IS CANNABIS SAFE?

Drug safety is evaluated by comparing risks to benefits in the treatment of certain conditions. Cannabis hasn't been evaluated for safety like this, but it has been extensively studied.

WHAT IS "PHARMACEUTICAL GRADE" CANNABIS, ANYWAY?

Put simply, it is cannabis that meets pharmaceutical standards, including being free from contaminants and being fully stable and standardized.

Bedrocan cannabis is within accepted contaminant levels for drugs that are meant to be inhaled. It has also been demonstrated to be fully standardized, meaning its Active Pharmaceutical Ingredients (like THC and CBD) are exactly the same within a narrow range, every time.

WHY DOES IT SEEM LIKE PEOPLE USE CANNABIS FOR SO MANY DIFFERENT ILLNESSES?

Anecdotal reports suggest that cannabis is used for a wide range of disorders. We're not sure what the actual effect on these conditions are. However, the active compounds in cannabis (called "cannabinoids") act on an internal system that is present in many, many different areas in our bodies. While its not fully understood, this system seems to work with the help of compounds produced by our bodies that are very similar to these cannabinoids, called "endocannabinoids". Read more on our **Science page**.

WHAT'S THE PROPER DOSE FOR CANNABIS?

No proper dosage for cannabis has yet been scientifically established. However, some useful information has been compiled by Health Canada. **Read that here**. In addition, you can read about

Bedrocan's research on **administration forms**, and information released by the Dutch Health Ministry: Information for Patients (OMC)

On Regulations

WHERE CAN I FIND MORE INFORMATION ON THE NEW MMPR?

Lots of information can be found on **Health Canada's website**.

WHAT IF I AM CURRENTLY AN MMAR PATIENT?

The MMAR will be completely phased out after April 1, 2014. Patients who are licensed under the MMAR can receive cannabis from a licensed producer under the new program. **Contact us for more information**.

HOW MUCH CANNABIS CAN I ORDER?

You can order as much cannabis as your doctor authorizes per day, multiplied by 30 days, up to a maximum of 150g per order.

IS MY MEDICINAL CANNABIS COVERED BY INSURANCE?

Generally, in Canada, medicinal cannabis is not yet covered by typical drug insurance plans. However it may be claimed under certain cases with the WSIB (Worker Safety Insurance Board in Ontario), as well as through Veterans Affairs, and can typically be claimed as a health deduction for personal income tax filing purposes.

CAN I TAKE MY CANNABIS ABROAD?

Most countries prohibit the use of cannabis. At this time, you cannot take your cannabis into such a country, *including the United States.*

ARE MEDICINAL CANNABIS REGULATIONS DIFFERENT IN OTHER COUNTRIES?

They are. **Click here** for a short review.

On Bedrocan

HOW MANY CANNABIS VARIETIES DO YOU HAVE?

To start, Bedrocan is introducing five different varieties to the Canadian market. **You can read about them here**.

HOW DO I REGISTER?

Information on registering with Bedrocan under the new MMPR can be found **here**.

CAN I BUY YOUR CANNABIS NOW?

Bedrocan aims to be processing patient orders for medicinal cannabis starting in February, 2014.

IS YOUR CANNABIS PRODUCED IN CANADA?

To bring Bedrocan varieties of medicinal cannabis to Canadian patients as quickly as possible, Bedrocan Canada currently imports cannabis varieties from the Netherlands. Throughout 2014 Bedrocan Canada aims to provide Canadian patients with fully regulated medicinal cannabis from the Dutch Health Ministry. We aim to produce Bedrocan varieties of medicinal cannabis in Canada starting in 2015.

WHAT DO I PAY FOR SHIPPING?

Bedrocan is pleased to offer free shipping on the first order of every month, up to the regulated maximum of 150g per shipment, or 30 days times the daily prescribed amount, whichever is the lower number.

HOW MUCH DOES BEDROCAN CANNABIS COST?

Bedrocan Canada's medicinal cannabis is priced at $7.50 per gram including shipping*

* Conditions apply: we offer one (1) free shipment per month.

HOW DOES BEDROCAN PROTECT MY PRIVACY AND KEEP MY INFORMATION SECURE?

Bedrocan takes your privacy very seriously. Please read our **privacy policy here**.

Careers

Canada Medicinal Cannabis

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Your Cart(0)

CANNA FARMS

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Menu...

Our Mission

Exceptional product at an excellent price, delivered with the best customer service.

Welcome to Canna Farms Ltd.

PATIENT REGISTRATION

Click here!

Established in 2014, Canna Farms a Licensed Producer under the MMPR, located in beautiful British Columbia.

Canna Farms is different from other licensed producers; *we are family owned and operated.* We also use ***traditional names of the strains we carry***; this way our clients can continue receiving strains that have worked for them in the past.

It is our mission to provide Canadian clients with the highest quality medicinal cannabis at the best possible price, grown with the highest standards in the industry.

We are proud to grow our product in a newly built, state-of-the-art facility. We are passionate about growing our product with exceptionally high standards, improving access to medical marijuana to all Canadian patients, and serving them with unmatched customer service.

We invite you to register with us!

LATEST NEWS

Registration & Pre-Ordering Open January 31st!

posted on January 28, 2014

STRAINS IN PRODUCTION - More Info to Come Very Soon!

Pure Kush **(AVAILABLE MAY 30, 2014)**

TBA

Master Kush **(AVAILABLE APRIL 15, 2014)**

TBA

Superbud **(AVAILABLE MAY 30, 2014)**

TBA

Red Cherry Berry **(AVAILABLE MAY 15, 2014)**

TBA

Crimea Blue **(AVAILABLE MAY 15, 2014)**

TBA

Green Crack **(AVAILABLE MAY 15, 2014)**

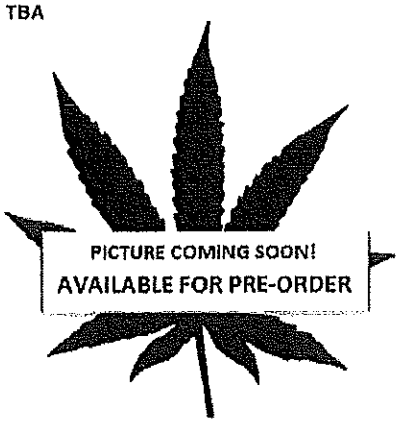
TBA

Kootenay Star **(AVAILABLE MAY 15, 2014)**

TBA

New York Diesel **(AVAILABLE MAY 15, 2014)**

TBA

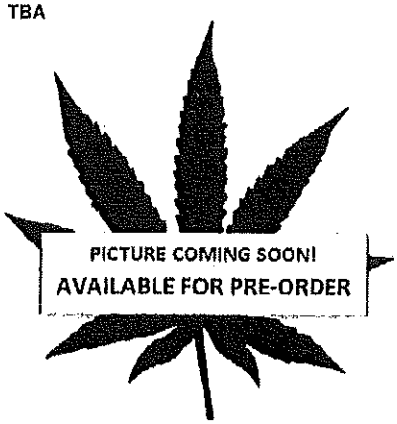


Rene **(AVAILABLE MAY 15, 2014)**

TBA

Drakensburg Gold **(AVAILABLE MAY 15, 2014)**

TBA



BC God Bud **(AVAILABLE MAY 30, 2014)**

TBA

Blueberry **(AVAILABLE MAY 30, 2014)**

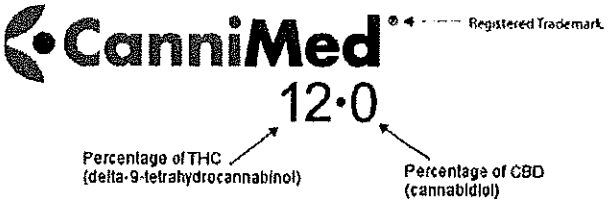
TBA

Helpful Links...

Our products

CanniMed® pharmaceutical-grade cannabis products are made from the flowering head, or "bud" of the female *Cannabis sativa spp. indica* plant. The cannabis plant material is dried under strict conditions to ensure proper curing of the herbal material while lessening the chance of contamination and fungal opportunity. Moisture content is monitored for consistency and to ensure appropriate usability and stability of the stored product. The cannabis plant material is milled to create a homogenous product for consistency of dosage. Dose consistency is required for research and therapeutic purposes, allowing the overseeing healthcare practitioner to be confident in the level of THC (delta-9-tetrahydrocannabinol) and/or CBD (cannabidiol) the patient is receiving.

CanniMed® pharmaceutical-grade cannabis products are packaged in child-proof tamper evident containers compliant with the Canadian Standards Association (CSA) and the Food and Drugs Act (FDA). CanniMed® product labels indicate the THC and CBD content for the product type, the packaging date and storage instructions.



Product options

CanniMed Ltd. is pleased to be a licensed producer under the Marihuana for Medical Purposes Regulations (MMPR). We are now shipping product to clients and are committed to maintaining supply without waiting lists or back orders for your critical medicine

	THC (delta-9-tetrahydrocannabinol) Content	CBD (cannabidiol) Content	Status
CanniMed 22·1	22.0%	0.7%	*Available February 15th!*

CanniMed 17·1	17.0%	0.7%	*Now Available*
CanniMed 12·0	12.5%	Less than 0.5%	*Now Available*
CanniMed 9·9	9.0%	9.5%	*Now Available*

Your safety and testing

CanniMed® products are produced in a controlled environment to ensure consistency of each lot. The plants are grown without the use of pesticides Inputs, including irrigation water and growing medium, are tested. Plant health and eventual material quality are a direct result of consistent, safe inputs

CanniMed® products are irradiated for patient benefit. Gamma irradiation, at food-safe levels, minimizes the risk that clients, especially immunocompromised clients, might be exposed to potentially harmful bacteria. This ionizing radiation is a recognized and reputable control process that does not alter the chemical properties of the dried marijuana products.

Each CanniMed® product is thoroughly tested to meet requirements of the Food and Drugs Act for:

- *appropriate cannabinoid concentration (THC and CBD)*
- *moisture level, or "water activity," to ensure appropriateness for stability and usability*
- *microbial purity (total bacterial and fungal activity), ensuring the product is free of E. coli, Salmonella and S. aureus*
- *the presence of any metals and mycotoxins (Aflatoxin B1, B2, G1, G2 and Ochratoxin A)*

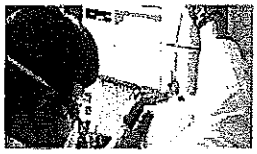
CanniMed® pharmaceutical-grade cannabis products must pass a rigorous release process to ensure that these specifications are met. Product that does not meet these stringent quality requirements is not released for client use. Our products are traceable from the starting plant material up to the client package assigned lot numbers in the unlikely event of a recall

Pricing and product sizes

CanniMed® products are available in 10 gram and 30 gram amounts. Product prices range from $7.50 to $12 per gram. Clients will have a choice for shipping at a Canada-wide flat rate ranging from $13.50 - $25.00. All product shipments are discretely packaged and require adult signature for delivery.

CanniMed production process

Learn More >



Our commitment to quality

Learn More >

Suggested dosing

Learn More >

Delivery options

Learn More >

Latest news

CanniMed Ltd. Congratulates Veterans Affairs Canada for Continued Coverage of Medical Marijuana under the New MMPR Program

January 10, 2014

CanniMed Ltd. Fulfilling Client Orders with First Shipment of Medical Marijuana

November 05, 2013

Prairie Plant Systems Responds To Cannabis Culture Coverage

October 11, 2013

See all >

1 Plant Technology Road, Box 19A, RR#5
Saskatoon, Saskatchewan, S7K 3J8 Canada

1-855-787-1577

Info@cannimed.com

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CanniMed®

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Menu...

ur Vision

r vision at CanniMed Ltd is to help people with chronic and terminal illnesses improve their quality of e when conventional medicine just isn't enough. We focus on producing pharmaceutical-grade cannabis rough research and development. **Learn More >**

News update

We have listened to feedback from our patients and a subset of them have requested higher THC lines. In response, we are pleased to announce the introduction of **CanniMed 22•1** (22% THC and 0.7% CBD). CanniMed 22•1 will become **available February 15, 2014.** We appreciate your suggestions and shared experiences. This helpful dialogue shapes our efforts in research to develop improved products for better symptom relief.

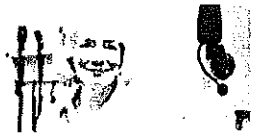
More great news! **CanniMed 12•0** (12.5% THC and less than 0.5% CBD) is now at **$ 7.50 per gram effective immediately.** We hope this new pricing will help patients with the transition to CanniMed Ltd. under the *Marihuana for Medical Purposes Regulations (MMPR).*

Our products

CanniMed® pharmaceutical-grade cannabis products are made from the flowering head, or "bud" of the female Cannabis sativa spp. indica plant. The cannabis plant material is dried under strict conditions to ensure proper curing of the herbal material while lessening the chance of contamination and fungal opportunity.

Learn More >

Application process



Only persons who have a medical document, signed by a medical practitioner, may legally obtain and use a designated amount of dried medical marijuana for their condition.

Learn More >

Latest news

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See all >

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Saskatoon, Saskatchewan, S7K 3J8 Canada

1-855-787-1577

Info@cannimed.com

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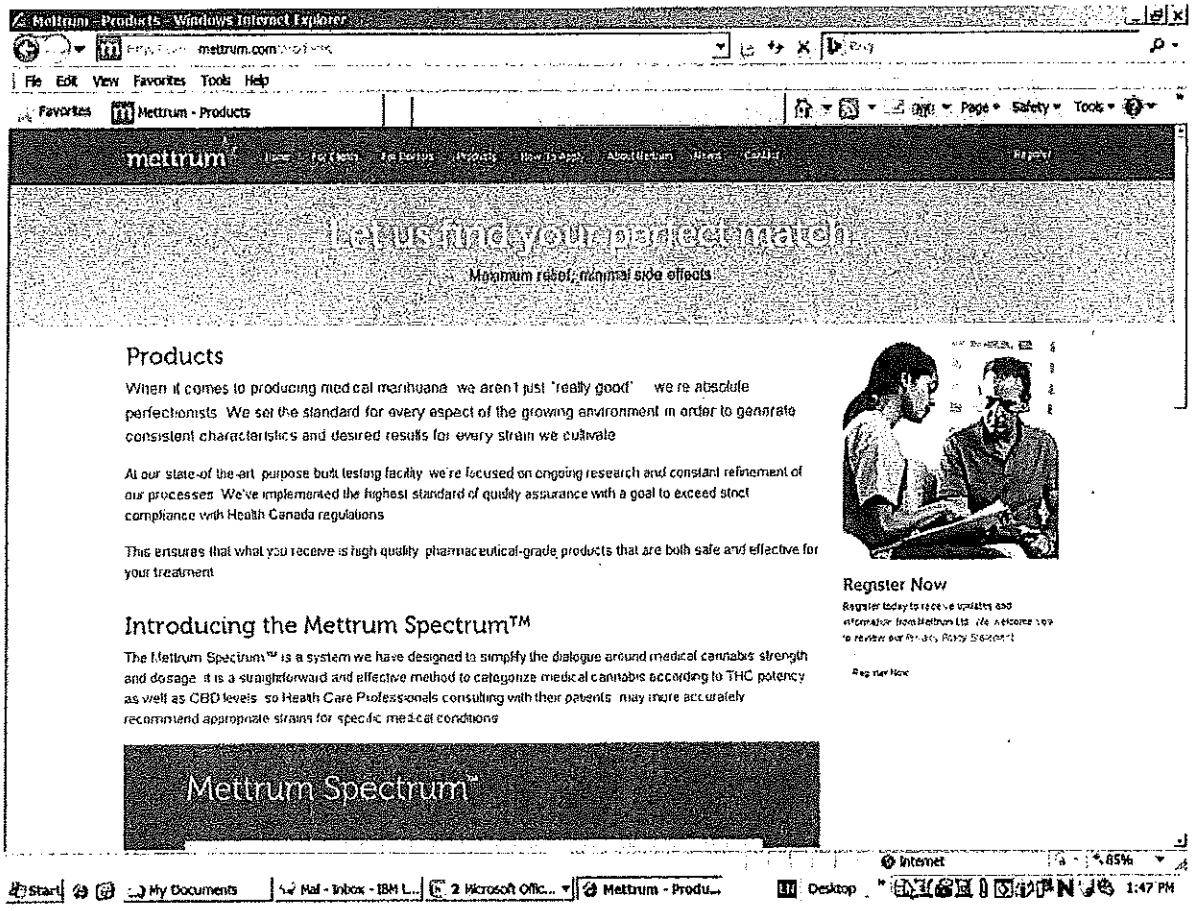
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Tools
mettrum
Let us find your perfect match.
Maximum relief, minimal side effects
Products
When it comes to producing medical marihuana we aren't just 'really good' we're absolute perfectionists We set the standard for every aspect of the growing environment in order to generate consistent characteristics and desired results for every strain we cultivate
At our state-of the-art purpose built testing facility we're focused on ongoing research and constant refinement of our processes We've implemented the highest standard of quality assurance with a goal to exceed strict compliance with Health Canada regulations
This ensures that what you receive is high quality pharmaceutical-grade products that are both safe and effective for your treatment
Introducing the Mettrum Spectrum™
The Mettrum Spectrum™ is a system we have designed to simplify the dialogue around medical cannabis strength and dosage It is a straightforward and effective method to categorize medical cannabis according to THC potency as well as CBD levels so Health Care Professionals consulting with their patients may more accurately recommend appropriate strains for specific medical conditions
Mettrum Spectrum™
Register Now
Register today to receive updates and
Internet
65%
Start
My Documents
Mail - Inbox - IBM L...
2 Microsoft Offic...
Mettrum - Produ...
Desktop
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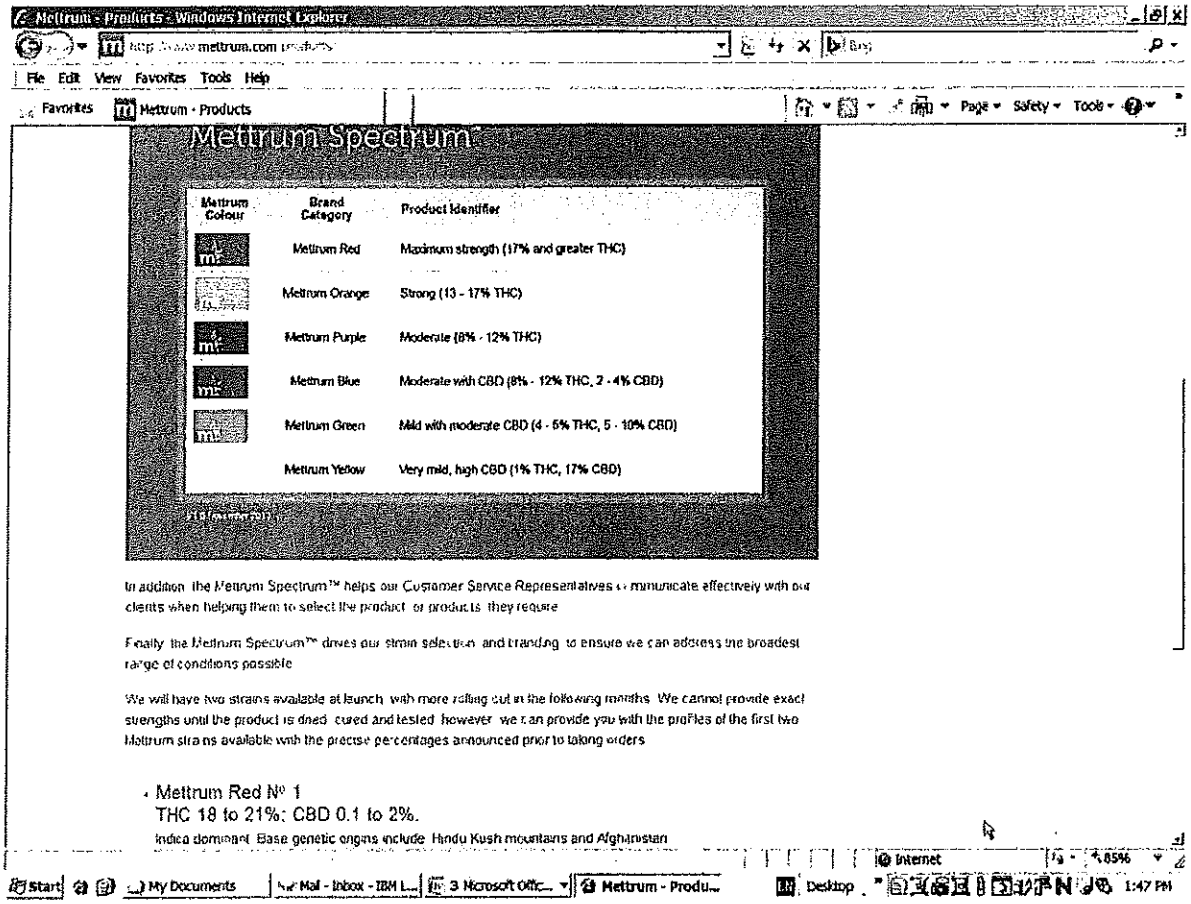
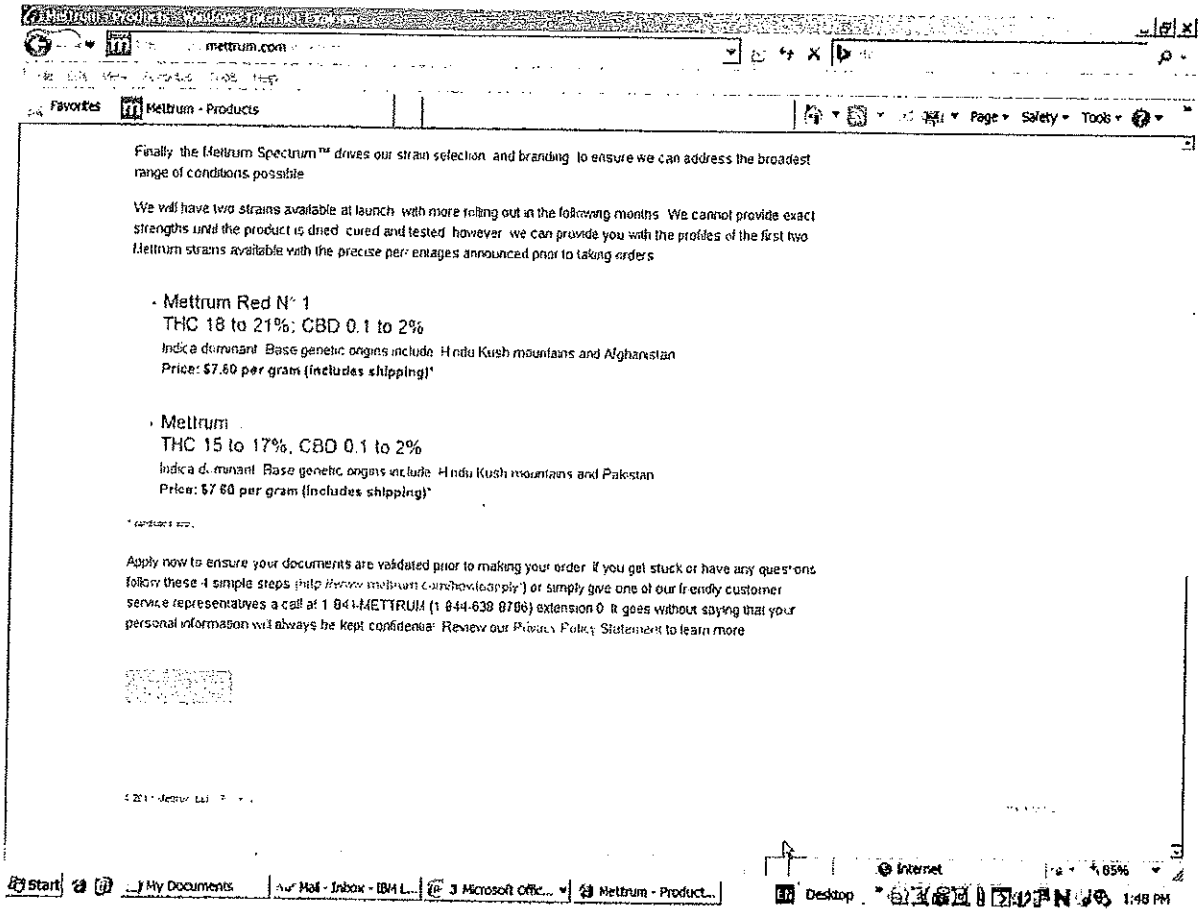

Mettrum - Products - Windows Internet Explorer
File Edit View Favorites Tools Help
Favorites
Mettrum - Products
Page Safety Tools
Mettrum Spectrum™
Mettrum Colour
Brand Category
Product Identifier
Mettrum Red
Maximum strength (17% and greater THC)
Mettrum Orange
Strong (13 - 17% THC)
Mettrum Purple
Moderate (8% - 12% THC)
Mettrum Blue
Moderate with CBD (8% - 12% THC, 2 - 4% CBD)
Mettrum Green
Mild with moderate CBD (4 - 6% THC, 5 - 10% CBD)
Mettrum Yellow
Very mild, high CBD (1% THC, 17% CBD)
In addition the Mettrum Spectrum™ helps our Customer Service Representatives communicate effectively with our clients when helping them to select the product or products they require
Finally the Mettrum Spectrum™ drives our strain selection and branding to ensure we can address the broadest range of conditions possible
We will have two strains available at launch with more rolling out in the following months. We cannot provide exact strengths until the product is dried cured and tested however we can provide you with the profiles of the first two Mettrum strains available with the precise percentages announced prior to taking orders
Mettrum Red № 1
THC 18 to 21%; CBD 0.1 to 2%.
Indica dominant. Base genetic origins include Hindu Kush mountains and Afghanistan
Internet
100%
Start
My Documents
Mail - Inbox - IBM L...
3 Microsoft Offic...
Mettrum - Produ...
Desktop
1:47 PM



Finally the Mettrum Spectrum™ drives our strain selection and branding to ensure we can address the broadest range of conditions possible

We will have two strains available at launch with more rolling out in the following months We cannot provide exact strengths until the product is dried cured and tested however we can provide you with the profiles of the first two Mettrum strains available with the precise percentages announced prior to taking orders

- Mettrum Red N° 1
  THC 18 to 21%; CBD 0.1 to 2%
  Indica dominant Base genetic origins include Hindu Kush mountains and Afghanistan
  Price: $7.60 per gram (includes shipping)*

- Mettrum
  THC 15 to 17%, CBD 0.1 to 2%
  Indica dominant Base genetic origins include Hindu Kush mountains and Pakistan
  Price: $7.60 per gram (includes shipping)*

* conditions apply.

Apply now to ensure your documents are validated prior to making your order If you get stuck or have any questions follow these 4 simple steps (http://www.mettrum.com/how/apply/) or simply give one of our friendly customer service representatives a call at 1 844-METTRUM (1 844-638 8786) extension 0 It goes without saying that your personal information will always be kept confidential Review our Privacy Policy Statement to learn more

Frequently Asked Questions

How has access to Medical Cannabis changed in Canada?

As of October 1, 2013 a new and improved medical Cannabis program (MMPR) became available to eligible Canadians who may gain access to medicinal Cannabis through receipt of a medical document (like a prescription) from their Doctor or Nurse Practitioner. Both the current "licenced to possess and produce" MMAR Canadians and new MMPR Canadians will be able to select a Licenced Producer to fulfill their prescribed monthly quantities. This is the beginning of a transition period that will eliminate personal production of medicinal Cannabis by individuals or designated growers in Canada. This transition process will end March 31, 2014.

Is Medical Cannabis safe?

Our products adhere to strict quality control standards and are tested for any possible contaminants. They undergo testing to determine accurate levels of metabolites (active ingredients). All of our products are assigned lot numbers, which allows us to recall our product and inform any affected clients quickly in the very unlikely event of a problem. Patient safety is top priority at The Peace Naturals Project.

What is the proper dosage for me?

Our philosophy at The Peace Naturals Project is that patients should use the minimum amount of medicine necessary to provide relief from their symptoms. Studies suggest that the average dose of medical cannabis is 1 to 3 g/d when vaporized or smoked. This number can be influenced by diet and lifestyle factors as well as a patient's particular condition.

How much will my medicine cost?

Our products are sold in 5 gram increments and are priced per gram. A minimum order is 15 grams. Our varieties, no matter which you choose, will be priced at $6 per gram.

Do you offer more than one variety?

We have several varieties of Cannabis, each with a different metabolic (active ingredient) profile. We will offer 12 varieties to start and are actively conducting research to be able to suggest varieties for specific ailments or symptoms.

How much product can I order at one time?

A maximum of 30 times your daily prescription amount or 150 grams, whichever is the lesser.

How can I begin to order my medicine from Peace Naturals?

In order to participate in the Peace Naturals Project Inc. client orientation program, you must first be entered into our carefully assembled program to ensure medicinal Cannabis consumers are provided the best information to make an informed decision once access to our purchase site is provided. In order to gain

"member" access, we must receive the appropriate Peace Naturals application form and medical document as well as a copy of the Consent to Disclose Medical Information.

Providing an email address in your application will enable you to use our secure section of our site where you can place your order online. Alternatively, you may call The Peace Naturals Project Inc. at 1-**888 64-PEACE (73223)** to place a verbal order or to request a Peace Naturals Product Order Form to be emailed, faxed or mailed to you. Please mail or courier the completed Peace Naturals Product Order Form to The Peace Naturals Project Inc. Visa, MasterCard and Debit Payments are accepted for online and telephone orders. Only certified cheque and money orders payable to The Peace Naturals Project Inc. are accepted for mail orders. **Please do not send cash in the mail.** Upon approval of your order, your product will be shipped to you.

Under the MMAR (Marihuana Medical Access Regulations), I had a license to possess/grow marijuana for medical purposes. With the new changes to the legislation, how do I become a client of The Peace Naturals Project Inc.?

The Health Canada-issued authorization documentation can be forwarded to The Peace Naturals Project Inc. We will add you to our client base and give you a unique client number as if you had applied. Please note that the documentation from Health Canada has expiry dates that will be upheld.

Upon your registering with The Peace Naturals Project Inc., or any other Licensed Producer, Health Canada will revoke the Authorization to Possess and any associated license to produce that it previously granted to you.

Is my medicine covered by my medical plan?

At this time most medical plans will not cover medical cannabis costs. If you are a veteran, you may have coverage through Veterans Affairs Canada. Medicinal Cannabis is regulated under the Narcotic Control Regulations and the Controlled Drugs and Substances Act but it does not have a Drug Identification Number (DIN) which is required for provincial and third-party formularies (medical plans). Medical cannabis expenses can be claimed on your income tax return under the Medical Tax Credit.

PEACE NATURALS QUICK LINKS:
About Us
Learning Centre
Contact Us Video Education Health & Medical Strains & Varieties Agronomics
Facebook.com/PeaceNaturals
Twitter.com/PeaceNaturals
Instagram.com/PeaceNaturals

Toll Free: 1(888) 64-PEACE (73223)

General Inquiries: info(at)peacenaturals.com

Media Inquiries: media(at)peacenaturals.com

www.peacenaturals.com

Important message:

Online ordering will be available within Canada for registered clients.

Interested in becoming a registered client? LEARN MORE

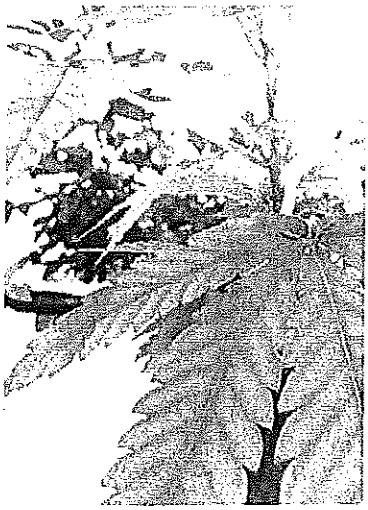
Our Products Can Only Be Viewed By Those Who Have An Online Account

THE PEACE NATURALS PROJECT SELF-CARE SOLUTION: MAKING LIVES A LITTLE BIT BETTER

Medical Cannabis has been shown to provide a range of medicinal benefits to patients with a number of serious illnesses, including multiple sclerosis, spinal cord injuries, asthma and arthritis, among others. Medical benefits include, but are not limited to pain relief, muscle relaxation, decreasing nausea and increasing appetite. The Peace Naturals Project offers a range of Cannabis flower solutions with varying degrees of active components known to be effective in different self -care scenarios, including varieties with non-psychoactive effects. Our products are not designed to eliminate underlying medical conditions. Our mission is to make our customers' lives a little bit better as they deal with those conditions.

Please click here to create or login to your account in order to view our varieties

Please note: The Federal guidelines currently require that new Licensed Producers perform a validation check before displaying variety information. We apologize for any inconvenience. Please take a moment to create an online account and our variety list will then be available to you.



PEACE NATURALS QUICK LINKS:

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Instagram.com/PeaceNaturals

Toll Free: 1(888) 64-PEACE (73223)

General Inquiries: info(at)peacenaturals.com

Media Inquiries: media(at)peacenaturals.com

www.peacenaturals.com

We're here to help. If you don't see an answer to your question, please [illegible]

Obtaining Medical Marijuana | Why Choose Tweed | Financial Assistance | General

Obtaining Medical Marijuana

Is Medical Marijuana legal?

Yes. In 2001, Canada legalized the use of medical marijuana. Until recently, those with Health Canada approval were allowed to grow marijuana for their personal use, designate some obtain medical marijuana directly from Health Canada.

In June 2013, Health Canada issued new regulations (the Marihuana for Medical Purposes Regulations, or MMPR) to replace government supply and homegrown medical marijuana v regulated commercial operations. The new medical marijuana regime will replace the old system as of April 1, 2014.

Tweed is one of several companies seeking to provide safe, quality medical marijuana under a Health Canada license.

I am new to medical marijuana. How can I register with Tweed?

Health Canada's website

the coming weeks we will be providing a helpful "how to" for to guide potential Tweed customers through the process.

That said, the process is actually pretty straight-forward:

1. Inform yourself of the benefits and drawbacks of medical marijuana

   Health Canada provides the following summary, which is a good place to start:

About FAQ Register Tweed Contact News Blog

3. Obtain a Medical Document from your doctor. Similar to a prescription, this document outlines the quantity of marijuana you are to take daily.
4. Register with Tweed by providing a copy of your Medical Document and completing our Registration Form

   We're not yet able to accept new patients, but as soon as we can we will provide both the Medical Document and Registration Form to patients and offer step-by-step support alo
5. Buy your medical marijuana online.

   Once registered, you will be given a Tweed ID that will let you access our online store to purchase directly over your computer. You can also order by phone. Tweed will discree directly to your door as quickly as possible. Throughout the entire process you will be able to get as much or as little help with product selection and with any other questions you

Does Tweed already have its license?

We sure do.

When will medical marijuana be available from Tweed?

Tweed is working hard to have a wide variety of medical marijuana available in April 2014. We will give specific updates on timing for each of our strains in the coming weeks

I have an Authorization to Possess under the old medical marijuana regime. Can I use this to obtain medical marijuana from Tweed?

If your Authorization to Possess card contains a "Valid until" date then you can submit that card in its original form in place of the new Medical Document. Tweed will then provide y documentation for possession, which will be valid until the same "Valid until" date.

It is important to be aware that once you provide your ATP to a Licensed Producer, you can no longer participate in the previous medical marijuana regime. Tweed recommends proce registration process but holding on to your ATP right until the end of March to make sure you maintain access to your medicine throughout this transition period. Once you submit you everything else already in place to immediately register you and begin providing access to our exceptional collection of strains

Do I have to smoke medical marijuana?

No. While some patients may choose to smoke medical marijuana, others use the dried marijuana in teas, food, or a vaporizer. In fact, Health Canada recommends that patients not co smoking.

Tweed will make further information on the various consumption methods available on its website in the coming weeks

What is a vaporizer and how does it work?

Vaporization heats up the medical marijuana to a point where the essential oils containing the medical ingredients are released, but combustion or "burning" of the dried plant material

Tweed is working with selected partners to provide high quality vaporizers to our patients at a discounted price through our online store

^

Why Choose Tweed?

Tweed will treat each customer with the utmost courtesy, empathy and respect, while offering the most extensive variety of high-quality medicinal cannabis strains in Canada

For an introduction to our company, please check out our

How many strains of medical marijuana will Tweed be selling?

Each strain of medical marijuana is unique. Some of the factors that impact whether a particular strain may be right for you include:

The levels of THC and CBD. THC and CBD are the two major medicinal components in marijuana, and must be clearly and accurately labeled. Generally speaking, THC provides psy CBD provides non-psychoactive effects. One combination of THC and CBD may be suitable to help patients with severe arthritis, while another may be more effective for patients suf

Whether the plant is a Sativa or Indica breed: Sativa and Indica are the two main types of cannabis plants, though there are also Sativa-Indica hybrids. Generally speaking, Indica is pe heavier, evening type of high that best addresses pain, insomnia, anxiety and similar types of ailments. Sativa, on the other hand, is generally viewed as providing a daytime, energetic effective at dealing with ailments such as depression.

Finding the right product for your condition may require sampling a variety of strains. However, Tweed will be there to provide personal and online support throughout the entire selec have the information and support that you need to find the strain that is best for you

Does Tweed sell edibles, oils or other derivative products?

No. Currently the Health Canada regulations restrict licensed producers to selling only dried marijuana.

Does Tweed mill or grind or irradiate its product?

No. Tweed intends to harvest the bud from the plant and provide it to patients in that form.

Is Tweed going to be using pesticides?

No. Tweed will not be using any form of pesticide

How many quality control checks will be in place to ensure Tweed only offers the best quality product?

Tweed will have well over 300 quality control checks in place to track production from seed to sale and ensure that everything we provide is of the highest and safest quality, is accura reliable relief.

I am not sure how to approach my doctor for a medical document to obtain medical marijuana. Can you help me?

The conversation about whether medical marijuana is right for your condition is an important one that only your doctor can help you with. However, it is important that your doctor ha benefits and appropriateness of medical marijuana.

Tweed is undertaking efforts to educate the medical community, and will also be providing materials on its website that patients can give their doctor to keep them informed about the findings

Will Tweed offer special pricing for low-income patients?

By carrying a wide variety of medical marijuana strains, Tweed will be able to offer its product at a range of prices

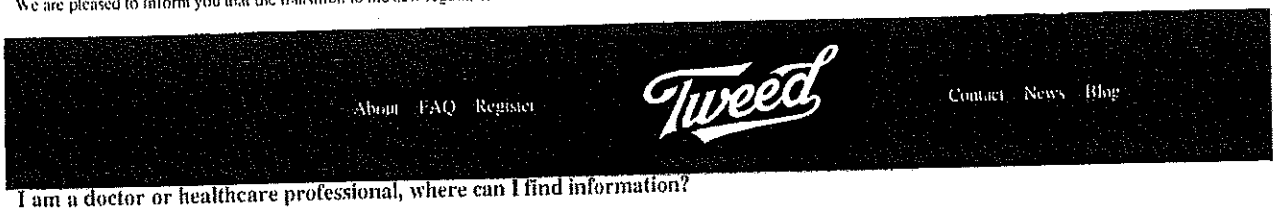
But we also understand that medical marijuana users may face financial challenges as a result of their condition To help our customers, Tweed will offer a its total production is priced under $5 per gram.

Is medical marijuana covered under health insurance programs?

Not yet, unfortunately

I am a veteran, how will my coverage change under the new regulations?

We are pleased to inform you that the transition to the new regulations will be seamless Please contact us for information about purchasing your medical marijuana from Tweed



I am a doctor or healthcare professional, where can I find information?

Tweed recognizes the importance of providing doctors with the information they need to make informed decisions about patient care

In the coming weeks we will be providing a variety of information and resources for the medical community to ensure doctors have the support they need

I am interested in working for Tweed, where can I send my resume?

Please visit our . drop us a line at work@tweed.com or sign up for updates from Tweed to keep informed of future job openings

Does Tweed have a privacy policy?

Yes. You can find it .

I am a local resident. What does this mean for Smiths Falls?

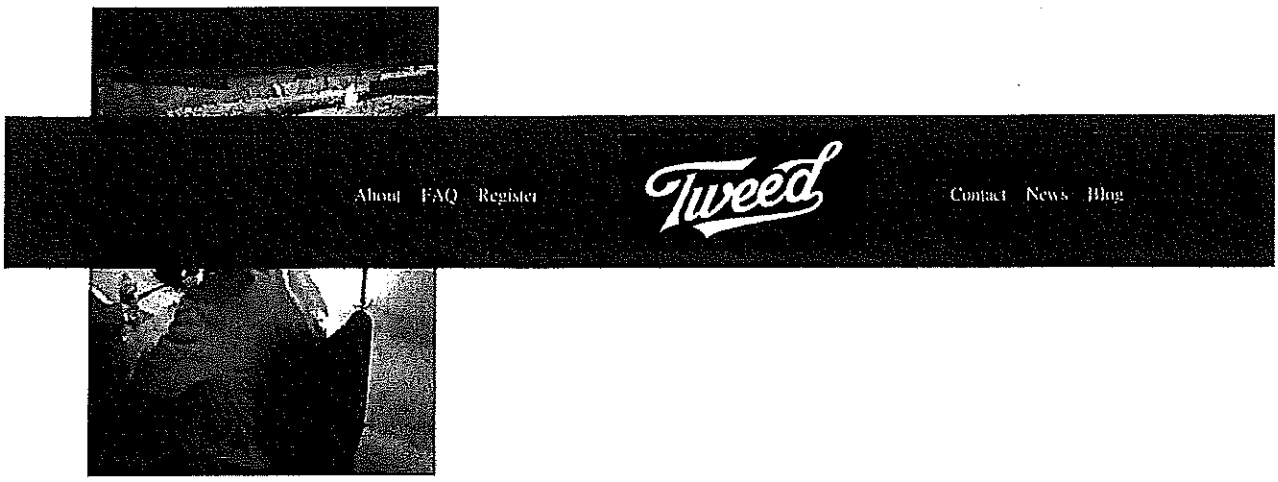
We think it means great things for Smiths Falls Our goal is to reinvigorate 1 Hershey Drive and bring new life back to this important landmark facility We will do this through direct operations, and by attracting new and diverse tenants to the site who, in turn, will also invest in the people and community of Smiths Falls

How many jobs will Tweed be creating?

At full capacity, Tweed anticipates a direct workforce of over 100 employees, as well as numerous spin-off jobs in areas such as construction.

Is there any reason to be concerned about safety in the Smiths Falls community?

No The operations of all licensed producers of medical marijuana will be highly regulated by the government to ensure every aspect of public safety and building security. Tweed wil security systems and protocols in place, and access to our product will be strictly limited to customers who have obtained a Medical Document from a licensed healthcare provider Th no marijuana will ever be available for direct purchase from the 1 Hershey Drive facility All sales are made discreetly by phone or online with products being delivered across Canad


About FAQ Register
Tweed
Contact News Blog

Everyone's financial situation is unique, and at Tweed we understand that

This is why we're proud to offer our customers a Compassionate Pricing Program to help you afford the medicine you need

Program Highlights

- 10% of Tweed production will be priced at $5 per gram or less, including shipping costs

- 20% discount for eligible* customers

*Eligibility

In order to qualify for the 20% discount, you must submit one of the following with your registration. *Tweed knows how important your privacy is, so once we verify your documents they are destroyed and not kept on file.*

a) Proof of receipt of financial assistance from either a federal or provincial program (see Appendix A for list of accepted programs), or

b) Copy of "Notice of Assessment" from Canada Revenue Agency indicating your income falls below $29,000 (see Appendix B for an explanation of why we chose this cut-off level).

Due to the nature of this program, Tweed retains the right to request this information on a yearly basis

Appendix A

Federal Programs

- Employment Insurance (EI) Sickness Benefits
- Employment Insurance (EI) Regular Benefits
- War Veterans Allowance (WVA)
- Old Age Security (OAS)
- Guaranteed Income Supplement (GIS)
- Income Assistance Program

Provincial Programs

- Alberta Seniors Benefit (ASB)
- Alberta Works – Income Support
- Assured Income for the Severely Handicapped (AISH)
- Special Needs Assistance for Seniors

British Columbia

- Employment and Income Assistance Program
- 55 Plus Program
- Income Assistance for Persons with Disabilities

Ontario

- Ontario Works
- Guaranteed Annual Income System for Seniors
- Ontario Disability Support Program (ODSP) Income Support

New Brunswick:

- Social Assistance Program

Newfoundland and Labrador

- Income Support Program

Northwest Territories

- Income Assistance

Nova Scotia

- Income Assistance (IA) Program

Nunavut

- Income Support Program

Prince Edward Island.

- Social Assistance Program

Quebec

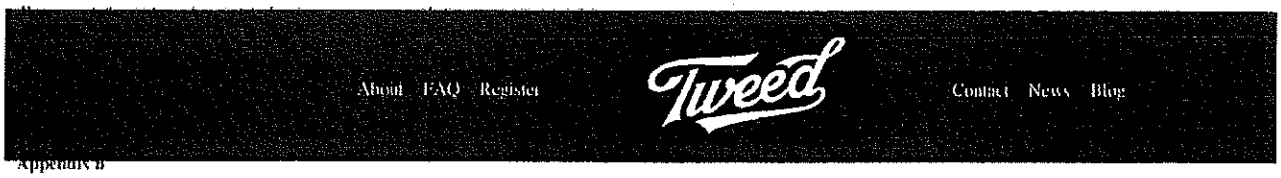
- Social Assistance Program
- Social Solidarity Program

Saskatchewan

- Saskatchewan Assistance Program
- Saskatchewan Employment Supplement
- Seniors Income Plan
- Saskatchewan Assured Income for Disability (SAID)

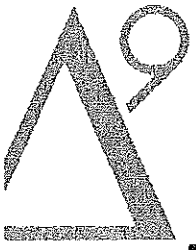
Yukon

- Social Assistance



Appendix B

Tweed selected $29,000 as our cut-off for assistance based on Statistics Canada before-tax low-income cut-off statistics. Although Statistics Canada uses family income to assess whet Canadians, Tweed will not ask patients to submit family income. We have chosen to apply an individual-based threshold of $29,000, which is equivalent to the low-income threshold f living in a major metropolitan area. Please see for more information



Delta 9 Bio-Tech

OUR MISSION:

Delta 9 Bio-Tech is committed to creating sustainable and standardized production practices that produce only the highest quality in medical cannabis products. We will strive to provide our patients with superior customer service, continuing and supportive education materials, and reliable and compassionate care. Our goal is to raise awareness about the medicinal benefits of cannabis, bridging the gap between anecdotal benefits and research supported evidence-based medicine.

Please send all inquiries to: info@delta9.ca

This is **Exhibit " E "** referred to in the
Affidavit of **TODD CAIN**
Affirmed before me
at the City of Ottawa,
in the Province of Ontario,
this 7th day of February 2014.

A Notary Public in for the Province of Ontario

Information for Health Care Professionals

Marihuana (marijuana, cannabis)
dried plant for administration by ingestion or other means
Psychoactive agent

This document has been prepared by the Controlled Substances and Tobacco Directorate at Health Canada to provide information on the use of marihuana for medical purposes. **Marihuana is not an approved therapeutic product and the provision of this information should not be interpreted as an endorsement of the use of this product, or marihuana generally, by Health Canada.**

Despite the similarity of format, it is not a Drug Product Monograph, which is a document which would be required if the product were to receive a Notice of Compliance authorizing its sale in Canada. This document is a summary of peer-reviewed literature and international reviews concerning potential therapeutic uses and harmful effects of marihuana. It is not meant to be comprehensive and should be used as a complement to other reliable sources of information.

This document should not be construed as expressing conclusions from Health Canada about the appropriate use of marihuana for medical purposes.

Marihuana (marijuana, cannabis) is not an approved therapeutic substance in Canada and no marihuana product has been issued a notice of compliance by Health Canada authorizing sale in Canada.

Prepared by Health Canada; previous version edited by CPhA

Date of latest version: September 2010

TABLE OF CONTENTS

1.0 Chemistry

1.1 Composition

Marihuana (Marijuana) is the common name for *Cannabis*, a hemp plant that grows throughout temperate and tropical climates (1). Although the leaves and flowering tops of *Cannabis* plants yield more than 60 different phyto-cannabinoids, the major active components are delta-9-tetrahydrocannabinol (Δ^9-THC, THC), cannabinol (CBN) and cannabidiol (CBD) (2). Other cannabinoids found in marihuana include cannabigerol (CBG), cannabichromene (CBC) and many others (3). In the living plant, these phytocannabinoids exist primarily as inactive monocarboxylic acids; heating triggers their decarboxylation and results in biological activation (4,5).

Δ^9-THC is the best studied cannabinoid and is responsible for most of the physical and psychotropic effects of cannabis (6). Other cannabinoids (such as CBD, CBC, CBG) are present in lesser amounts in the plant and have little if any psychotropic properties (6). It is reasonable to consider about 10% (range 1-30%) as an average for THC content in cannabis found on the illicit market in Canada (internal communication). The marihuana provided by Health Canada is comprised of the mature flowering heads of female plants and contains 12.5 ± 2% total THC (Δ^9-THC and Δ^9-THC acid) and less than 0.5% CBD, CBG, CBN, CBC (7). The MS-17/338 production line has THC concentrations typically higher than 10%, with the mature flowering heads containing the highest concentration of THC (7). The plant is cultivated and harvested in compliance with Good Manufacturing Practices, by Prairie Plant Systems Inc. under contract to Health Canada (8). The product is irradiated to ensure that users whose immune systems may be compromised are not exposed to toxic spores which occur naturally in the plants (7).

1.2 Other ingredients

Marihuana smoke contains many of the same carcinogenic chemicals found in tobacco smoke (2,9,10). However, differences in the smoking techniques used by marihuana and tobacco smokers are reported to result in three-fold higher levels of tar and five-fold higher levels of carbon monoxide being retained in the lungs during cannabis smoking compared to tobacco smoking (11). This greater retention of tar and carbon monoxide from cannabis smoke may compensate for the fact that a marihuana smoker typically smokes fewer cigarettes per day than a tobacco smoker (i.e., the exposure to tar and carbon monoxide could be similar for both groups of smokers) (12,13). A systematic comparison of the mainstream smoke composition from marihuana (Health Canada product) and tobacco cigarettes prepared in the same way and consumed in an identical manner under two different sets of smoking conditions ("standard" and "extreme") has been reported (10). The "standard" condition reflects typical tobacco cigarette smoking conditions, whereas the "extreme" condition approaches that typically seen in marihuana smoking (10). Ammonia in mainstream marihuana smoke was 20-fold greater than that found in tobacco smoke and oxides of nitrogen and hydrogen cyanide were 3-5 times higher than those in tobacco smoke. Carbon monoxide was significantly lower in mainstream marihuana smoke, under both smoking conditions. Tar was statistically significantly higher in mainstream marihuana smoke only under the "extreme" smoking condition.

1.3 Stability and storage

Most of the information on the stability of marihuana does not distinguish between THC and its carboxylic acid (THCA). The latter is degraded to THC by pyrolysis during smoking or in the inlet of gas chromatographs used in forensic analysis (14). Heat, light, humidity, acidity and oxidation all affect the stability of cannabis (15,16). The National Institute on Drug Abuse (NIDA) reports that retention samples of their carefully prepared and standardized cigarettes are stable for months, particularly when stored below 0°C (-18 °C) in the dark in tightly-closed containers (17). Even when stored at +18°C, only a third of the THC content is lost over a 5-year period with some increase in the concentration of CBN. Lower-potency cigarettes (1.15%) appear to lose more THC compared to higher potency cigarettes (2.87%) (17).

2.0 Clinical Pharmacology

2.1 Pharmacodynamics

Two types of cannabinoid receptors, CB_1 and CB_2, have been identified each with distinct patterns of tissue expression. CB_1 receptors are most abundant in nervous tissue but are also found in adipocytes, leukocytes, spleen, heart, lung, liver, pancreas, kidney, reproductive organs, skeletal muscle and skin; CB_2 receptors are most highly concentrated in the tissues and cells of the immune system such as leukocytes and spleen but can also be found to a lesser degree in bone, liver and also in some neurons (reviewed in (18) and also in (19)). Most tissues contain a functional

endocannabinoid system which consists of the cannabinoid receptors (CB_1 or CB_2), the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) and their "entourage" compounds which modulate endocannabinoid activity, and endocannabinoid synthesizing and degrading enzymes (20).

Much of the pharmacodynamic information on marihuana refers to the effects of the major constituent THC which has activity at both CB receptors but whose psychoactive effects are mediated by the CB_1 receptor (21). On the other hand, CBD lacks detectable psychoactivity but displays high potency as an antagonist of CB_1/CB_2 receptor agonists and affects the activity of a significant number of other targets including ion channels, receptors, and enzymes (reviewed in (22)). Results from pre-clinical studies suggest CBD has anti-inflammatory, analgesic, antipsychotic, anti-ischemic, anxiolytic, and antiepileptic effects (reviewed in (22)). CBN is a product of Δ^9-THC oxidation and has 10% of the activity of Δ^9-THC (22). Its effects are not well studied but it appears to have some immunosuppressive properties (23). CBG is a partial $CB_{1/2}$ receptor agonist and may have some anti-inflammatory and analgesic properties (24,22). Much of what is known about the beneficial properties of these non-pyschotropic cannabinoids was derived from *in vitro* and animal studies and few, if any, clinical studies of these substances exist. However, the results from these *in vitro* and animal studies point to potential therapeutic indications such as psychosis, epilepsy, anxiety, sleep disturbances, neurodegeneration, cerebral and myocardial ischemia, inflammation, pain and immune responses, emesis, food intake, type-1 diabetes, osteogenesis, and cancer (reviewed in (22)). For more in-depth information on the pharmacology of cannabinoids, the reader is invited to consult the following resources (25,22).

Table 1 (next page), adapted from the British Medical Association Report (2), notes some of the pharmacological effects of cannabis in the therapeutic dosage range. Many of the effects are biphasic, with increased activity with acute or smaller doses, and decreased activity with larger doses or chronic use (26,2). Effects differ greatly among individuals and may be greater in those who are severely ill, elderly, or those taking other drugs.

The acute effects of smoking marihuana include almost immediate euphoria (the marihuana "high") as well as cardiovascular, bronchopulmonary, ocular, psychological and psychomotor effects. Maximum euphoria occurs within 15 minutes after smoking; the psychological effects reach a plateau which can last for several hours (6). However, on first dosing, some people experience dysphoria and anxiety (27). The effects on the cardiovascular system (tachycardia, etc.) decline much faster as THC is distributed out of the circulatory system. Tachycardia is the most consistent of the physiological effects of marihuana (28,29).

The short-term psychoactive effects of marihuana smoking include the above-mentioned euphoria as well as relaxation, time-distortion, intensification of ordinary sensory experiences (such as eating, watching films and listening to music) and loss of inhibitions that may result in laughter (30). This is followed by a depressant period (31). While there is some inconsistency in reports regarding the acute effects of cannabis on memory and motor skills (32,33,34), most reviews note that marihuana use is associated with impaired function on a variety of cognitive and short-term memory tasks (35,31,23,36). The levels of THC in the plasma after smoking appear to have a dose and concentration dependent effect on cognitive function (37). Driving and operation of intricate machinery, including aircraft, may be significantly impaired (38,39,40,41).

Table 1: Pharmacologic actions of cannabis in humans (2)

Body System/Effect	**Detail of Effects**
Central Nervous System (CNS)	
Psychological	Euphoria ("high"), dysphoria, anxiety, depersonalization, precipitation or aggravation of psychosis.
Perception	Heightened sensory perception, distortion of space and time, sense, hallucinations, misperceptions.
Sedative	Generalised CNS depression, drowsiness, somnolence; additive with other CNS depressants.
Cognition, psychomotor performance	Fragmentation of thoughts, mental clouding, memory impairment, global impairment of performance especially in complex and demanding tasks.
Motor function	Increased motor activity followed by inertia and incoordination, ataxia, dysarthria, tremulousness, weakness, muscle twitching.
Analgesic	Similar in potency to codeine but by a different pharmacological mechanism.
Anti-emetic, increased appetite	With acute doses; effect reversed with larger doses or chronic use (tolerance).
Tolerance	To most behavioural and somatic effects, including the "high" (with chronic use).
Dependence, abstinence syndrome	Has been produced experimentally following prolonged intoxication: symptoms include disturbed sleep, decreased appetite, restlessness, irritability and sweating.
Cardiovascular System	
Heart rate	Tachycardia with acute dosage, bradycardia with chronic use.
Peripheral circulation	Vasodilation, conjunctival redness, postural hypotension.
Cardiac output	Increased output and myocardial oxygen demand.
Cerebral blood flow	Increased with acute dose, decreased with chronic use.
Respiratory System	
Ventilation	Small doses stimulate; larger doses depress.
Bronchodilation	Coughing, but tolerance develops.
Airways obstruction	From chronic smoking.
Eye	Decreased intraocular pressure.
Immune System	Chronic use: impaired bactericidal activity of macrophages in lung and spleen.
Reproductive System	
Males	Antiandrogenic, decreased sperm count and sperm motility (with chronic use, but tolerance may develop).
Females	Suppression of ovulation, complex effects on prolactin secretion; increased obstetric risk with chronic use.

2.2 Pharmacokinetics

This section will be restricted to human pharmacokinetics, mainly of smoked cannabis, but with some comparisons to oral THC, including dronabinol (Marinol®) and Sativex® (Δ^9-THC and CBD) as well as other routes of administration.

2.2.1 Absorption

2.2.1.1 Smoked cannabis

The amount of Δ^9-THC delivered from cannabis cigarettes is not uniform and is a major variable in the assessment of absorption (5). Uncontrolled factors include the source of the plant material and the composition of the cigarette, together with the efficiency and method of smoking used by the subject (42,5). Smokers often titrate their THC intake adapting their smoking behaviour to obtain desired levels of THC by taking more puffs and/or inhaling more efficiently depending on the strength of THC (43). THC absorption by inhalation is extremely rapid but quite variable, with a bioavailability of 2 to 56% through the smoking route depending on depth of inhalation, puff duration and breathhold (44,45). Standardised cigarettes have been developed by the National Institute on Drug Abuse (NIDA), and the relationships among cannabis THC content, dose administered and resultant plasma levels have been investigated. Smoking cannabis containing 1.64% THC (mean dose 13.0 mg THC) resulted in mean peak THC plasma levels of 77 ng/mL (46).

2.2.1.2 Vaporized cannabis

Vaporization of cannabis has been explored as an alternative to smoking. The advantages of vaporization apparently include the formation of a smaller quantity of toxic by-products such as carbon monoxide, polycyclic aromatic hydrocarbons (PAHs) and tar, as well as a more efficient extraction of THC from the cannabis material (47,48,49,43,50). The subjective effects and plasma concentrations of THC are comparable to those of smoked cannabis with absorption being somewhat faster with the vaporizer (43). The vaporizer is well-tolerated, with no reported adverse effects, and is generally preferred over smoking by most subjects (43). While vaporization is amenable to self-titration (49,43), the proper use of the vaporizer for optimal administration of medicinal cannabis has to be established in more detail (50). The amount and type of cannabis placed in the vaporizer, the vaporizing temperature and duration of vaporization, and the balloon volume are some of the parameters that can affect the delivery of THC (49). Bioequivalence of vaporization compared to smoking has not been established.

2.2.1.3 Oral THC

THC can be absorbed orally by ingestion of foods containing cannabis (butters, oils, brownies, cookies), teas prepared from leaves and flowering tops, or through ingestion of capsules containing THC or THC analogues. Absorption from an oral dose of 20 mg THC in a chocolate cookie was described as slow and unreliable (42), with a systemic availability of only 4 to 12% (46). While most subjects displayed peak plasma THC concentrations between 1 to 2 h, some of the 11 subjects in the study only peaked at 6 h and many had more than one peak. Consumption of cannabis-laced brownies containing 2.8% THC was associated with changes in behaviour although the effects were slow to appear and variable (51). Peak effects occurred 2.5 to 3.5 h after dosing. Modest changes in pulse and blood pressure were also noted. Tea made from dried cannabis flowering tops (19.1% THCA, 0.6% THC) has been documented, but the bioavailability of THC from such teas is likely to be smaller than that achieved by smoking (52). Only 10-20% of synthetic THC (dronabinol, Marinol®) administered in capsules with sesame oil enters the systemic circulation indicating extensive first-pass metabolism (53). The psychotropic effect or "high" occurs more quickly by the smoking than the oral route, which has been characterized by Iversen (54) as the reason "smoking is the preferred route of cannabis for many people".

2.2.1.4 Buccal THC

Following a single buccal administration of Sativex® (four sprays of Δ^9-THC 27mg/mL and CBD 25 mg/mL, totalling 10.8mg Δ^9-THC and 10 mg CBD), peak plasma concentrations of both THC and CBD typically occur within 2-4 h (55). When administered bucally, blood levels of THC and other cannabinoids are lower than those achieved by inhalation of the same dose of smoked cannabis because absorption is slower, redistribution into fatty tissue is rapid and some of the THC undergoes hepatic first-pass metabolism to 11-hydroxy-THC (55).

2.2.1.5 Rectal THC

Limited evidence suggests a higher bioavailability of THC by the rectal route than by the oral route due to higher absorption and decreased first-pass metabolism (56,57). In humans, rectal doses of 2.5-5.0 mg THC were associated with peak plasma levels of THC ranging from 1.1 to 4.1 ng/mL and 6.1 to 42.0 ng/mL hydroxy-THC within 2-8 h and 1-8 h (respectively) after administration (56). Data from animal studies indicate that in contrast to pure Δ^9-THC, rectal administration of the hemisuccinate ester of Δ^9-THC resulted in higher bioavailability of Δ^9-THC (52-61%) (58,59,60). Plasma concentrations of Δ^9-THC were dose and vehicle-dependent and also varied according to the chemical structure of the THC ester (59). In dogs, a dose of the hemisuccinate ester equivalent to 5 mg of Δ^9-THC yielded a peak mean plasma concentration of 27 ng/mL Δ^9-THC within an hour after administration; a 10 mg equivalent dose yielded a peak concentration of 118 ng/mL 2 h after dosing; a 20 mg dose gave a 190 ng/mL peak mean plasma concentration one hour after administration (59).

2.2.1.6. Topical THC

Cannabinoids are highly hydrophobic, making transport across the aqueous layer of the skin the rate-limiting step in the diffusion process (5). No clinical studies on the percutaneous absorption of cannabis-containing ointments, creams or lotions exist. However, some research has been carried out on transdermal delivery of synthetic and natural cannabinoids using a dermal patch (61,62). Mean steady-state plasma concentration of Δ^8-THC was 4.4 ng/mL within 1.4 h, and was maintained for at least 48 h (61). Permeabilities of cannabidiol (CBD) and cannabinol (CBN) were found to be 10-fold higher than for Δ^8-THC (63).

2.2.2 Distribution

Distribution of THC begins immediately after absorption where it is taken up primarily by fatty tissues and highly perfused organs such as the heart, lung, brain and liver (5). THC has a large apparent volume of distribution, approximately 10 L/kg, because of its high lipid solubility (64). The plasma protein binding of THC and its metabolites is approximately 97% (65,66). THC is mainly bound to low-density lipoproteins, with up to 10% present in red blood cells (67), while the metabolite, 11-hydroxy THC, is strongly bound to albumin with only 1% found in the free-fraction (68).

The highest concentrations of THC are found in the heart and in adipose tissue, with levels reaching 10 and 1000 times that of plasma, respectively (69). Despite the high perfusion level of the brain, the blood-brain barrier (BBB) appears to limit the access and accumulation of THC in this organ (70) and the slight delay in correlating peak plasma concentration to psychoactive effects may be attributed to the time required for THC to traverse this barrier (42).

THC accumulates and is retained in fatty tissue, and its release from this storage site into the blood is slow (70). It is not certain if THC persists in the brain in the long-term; however, the presence of acute cognitive deficits in abstinent heavy cannabis users raises the possibility that THC may be retained in the brain at least in the short term (71,72). One animal study suggested food deprivation or adrenocorticotropic hormone (ACTH) administration in rats accelerates lipolysis and the release of THC from fat stores, however further research is needed to determine if these effects are associated with intoxication or behavioural/cognitive changes (73).

2.2.3 Metabolism

Most cannabinoid metabolism occurs in the liver and different metabolites predominate depending on the route of administration (42,5). The complex metabolism of THC involves allylic oxidation, epoxidation, decarboxylation and conjugation (42). THC is oxidized by the xenobiotic-metabolizing cytochrome P450 (CYP) mixed-function oxidases 2C9, 2C19 and 3A4 (5). The major initial metabolites of THC are the active 11-hydroxy THC and the non-active 11-nor-9-carboxy THC (5). 11-hydroxy THC is rapidly formed by the action of hepatic microsomal oxidases, and plasma levels parallel the duration of observable drug action (74,75). 11-hydroxy THC has psychotomimetic properties equal to those of THC (76,77). The psycho-inactive 11-nor-9-carboxy THC is the primary acid metabolite of THC excreted in urine (78) and it is the cannabinoid often screened for in forensic analysis of body fluids (79,80).

Xenobiotics are not only metabolized by CYPs but they also modulate the expression level and activity of these enzymes; they are therefore a focal point in drug-drug interactions and adverse drug reactions (81). Polyaromatic hydrocarbons found in tobacco (and cannabis) smoke induce the expression of CYP1A2 (82) while THC, cannabidiol (CBD), and cannabinol (CBN) inhibit CYP1A1, 1A2 and 1B1 enzymes (83). CBD has also been shown to inhibit formation of THC metabolites catalyzed by CYP3A4, with less effect on CYP2C9 (64), albeit sufficiently to decrease the formation of 11-hydroxy THC (84).

While minimal information is available in the literature, results from some *in vitro* experiments indicate that THC also inhibits CYP3A4, CYP2C9 and CYP2C19, while CBD inhibits CYP2C19, although higher concentrations than those seen clinically are required for inhibition (55). Few studies have specifically evaluated cannabis-drug interactions. Therefore, although the clinical significance of potential metabolic interactions through these pathways has not been established, clinicians should carefully monitor patients who are concomitantly consuming cannabis and other medications that are metabolized by these enzymes. For example, the Sativex® product monograph cautions against combining Sativex® with amitriptyline or fentanyl (or related opioids) which are metabolized by CYP3A4 and 2C19 (55). Cannabis smoking as well as orally administered dronabinol may also affect the pharmacokinetics of antiretroviral medications (85). In addition, and as seen with tobacco smoke, cannabis smoke has the potential to induce CYP1A2, increasing the metabolism of xenobiotics biotransformed by this isozyme such as theophylline (86) or the antipsychotic medications clozapine or olanzapine (87). Further information on drug-drug interaction can be found in section 7.3.

2.2.3.1 Inhalation

Plasma values of 11-hydroxy THC appear rapidly and peak shortly after THC, at about 15 minutes after the start of smoking (88). Peak plasma concentrations are approximately 5%-10% of parent THC and the area under the curve (AUC) profile of this metabolite averages 10-20% of the parent THC (75). Similar results were obtained with intravenous THC administration (89).

Peak plasma values of 11-nor-9-carboxy THC occur 1.5 to 2.5 h after smoking and are about one third the concentration of parent THC (88). Following oxidation, the phase II metabolites of the free drug or hydroxy-THC appear to be glucuronide conjugates (42).

2.2.3.2 Oral

After oral doses of THC, parent THC and its active metabolite, 11-hydroxy-THC which is similar to or greater in potency than THC, are present in approximately equal concentrations in plasma (90,51). Concentrations of both parent drug and metabolite peak at approximately 2 to 4 h after oral dosing and decline over several days. Clearance averages about 0.2 L/kg-h, but is highly variable, due to the complexity of cannabinoid distribution (53). The plasma levels of active 11-hydroxy metabolite are about 3 times higher than observed in the plasma from smoking (75).

2.2.4 Excretion

THC levels in plasma decrease rapidly after cessation of smoking. Mean THC plasma concentrations are approximately 60% and 20% of peak concentrations 15 and 30 min post-smoking respectively (91) and are below 5 ng/mL 2 h after smoking (45). However, THC from a single dose can be detected in plasma for at least a day and up to 13 days in chronic smokers (92). The decline of THC in plasma is multiphasic and as Harvey (64) notes, the estimates of the terminal half-life of THC in humans have progressively increased as analytical methods have become more sensitive. While figures for the terminal elimination half-life of THC appear to vary, it is probably safe to say that it averages at least a week and could be considerably longer. Low levels of THC metabolites have been detected for more than 5 weeks in the urine and feces of cannabis users (64). The degree of THC use does not appear to influence the plasma half-life of THC (89).

Following inhalation (or intravenous administration), elimination of THC and its metabolites occurs via the feces (65%) and the urine (20%) (5). After five days, 80% to 90% of the total dose is excreted (75). Similarly, following oral doses, THC and its metabolites are excreted in both feces and urine (75). Biliary excretion is the major route of elimination with about half of a radiolabelled oral dose being recovered from the feces within 72 h in contrast to the 10 to 15% recovered from urine (75).

2.3 Pharmacokinetic-pharmacodynamic relationships

The temporal relationship between plasma concentrations of THC and the associated psychotropic, cognitive and motor effects is unclear (93,94). Furthermore, dose and plasma concentration versus response for possible therapeutic applications are ill-defined, except for some information obtained for oral dosing with dronabinol (synthetic THC) for its limited indications (53). Interpretations of the pharmacokinetics of THC are also complicated by the presence of active metabolites, particularly 11-hydroxy THC, which are found in higher concentrations after oral administration than after inhalation (90,51).

Target THC plasma concentrations have been derived based on the subjective "high" response that may or may not be related to the potential therapeutic applications. Various pharmacodynamic models provide steady-state blood plasma concentration estimates in the range of 7-29 ng/mL THC necessary for the production of a 50% maximal subjective "high" effect (93). Serum concentrations between 7 and 10 ng/mL (whole blood, approximately 3-5 ng/mL) have been compared to a blood-alcohol concentration of 0.05% which is associated with driver impairment (95). Simulation of multiple dosing with a 1% THC cigarette containing 9 mg THC yielded a maximal "high" at about 45 minutes after dosing, declining to 50% of peak at about 100 minutes following smoking (94). A dosing interval of 1 h with this dose would give a "continuous high" and the recovery after the last dose would be 150 minutes. The peak THC plasma concentration during this dosage is estimated at about 70 ng/mL and the steady-state THC plasma concentration at 50% of the maximum "high" effect ($C_{ss}(50)$) at about 30 ng/mL THC.

3.0 Dosing

Precise dosages for cannabis have not been established. The complex pharmacology of cannabinoids, interindividual differences in cannabinoid bioavailability, prior exposure to and experience with cannabis, the variable potency of the plant material, and different dosing regimens used in different research studies all contribute to the difficulty in reporting precise doses or establishing uniform dosing schedules (91,96). Nevertheless, some "rough" dosing guidelines for smoked or vaporized marihuana have been published (see below). Besides smoking and vaporization, marihuana is known to be consumed in baked goods such as cookies or brownies or drunk as teas or infusions. However, absorption by the oral route is slow and erratic (see section 2.2) and dosages are even less well established in these cases (51,97,98,52). Other forms of preparation reported in the lay literature include cannabis-based butters, oils, compresses, creams, ointments, and tinctures (99,6,100,101,102) but again, little or no dosing information exists here and much of the information is anecdotal in nature. Patients with no prior experience with marihuana and initiating marihuana therapy for the first time are cautioned to begin at a very low dose and to stop therapy if unacceptable or undesirable side effects occur.

3.1 Smoking

According to the World Health Organization (WHO) (103), a typical joint contains between 0.5 and 1.0 g of cannabis plant matter (average 750 mg) which may vary in THC content between 7.5 and 225 mg (i.e. typically between 1 and 30%; see Table 2). The amount of other cannabinoids present, mainly cannabinol (CBN) and cannabidiol (CBD), is usually much lower. The actual amount of THC delivered in the smoke varies widely and has been estimated at 20 to 70%, the remainder being lost through combustion or side-stream smoke (96). Furthermore, the bioavailability of THC (the fraction of THC in the cigarette which reaches the bloodstream) from the smoking route is variable (2-56%) and influenced by the smoking topography (the number, duration, and spacing of puffs, hold time and inhalation volume) (45). In addition, expectation of drug reward can also influence smoking dynamics (104). Thus, the actual dose of THC absorbed when smoked is not easily quantified.

Table 2: Relationship between THC percent in plant material and the available dose in an average joint.

% THC (mg per 100 mg cannabis)	mg THC per 750 mg * (" average joint")
1	7.5
2.5	18.75
5	37.5
10	75
15	112.5
20	150
30	225

* *WHO average weight*

Using a paced smoking protocol, the mean plasma concentration of THC after a first inhalation of a marihuana cigarette containing 3.55% THC has been reported to be 18.1 ng/mL (1.8-37.0 ng/mL) with the mean peak plasma concentration reaching 162 ng/mL (76-267 ng/mL) after 7 puffs or almost complete smoking of the cigarette (91,45). Peak plasma concentrations of THC in the range of 50-100 ng/mL associated with a subjective "high" (section 2.3) can thus be easily attained by smoking a single 3.55% THC marihuana cigarette (900 mg plant material, 32 mg THC) (91). A 750 mg joint of 5% strength (i.e., 37.5 mg THC) would yield slightly higher plasma levels. If the current average "street" marihuana contains 10% THC, then plants yielding joints from such a source might have an available 75 mg dose and could result in rapid attainment of plasma THC concentrations above 300 ng/mL. The availability of even more potent strains of marihuana would yield even higher plasma concentrations of THC.

There are few, if any, efficacy studies on the amounts of cannabis required for a therapeutic effect. However, one recent Canadian study showed that a single inhalation of a 25 mg dose of smoked marihuana (THC content 9.4%) yielded a mean plasma THC concentration of 45 ng/mL within 2 minutes after initiating smoking (105). Various surveys have reported that people using smoked cannabis for medical purposes used between 10-20 grams of cannabis per week or approximately 1-3 grams per day (96,106,107). Assuming cannabis with 15% THC, this would suggest an intake between 34-68 mg of THC per day (96).

3.2 Oral
The pharmacokinetic information described in section 2.2 reports the erratic and slow absorption of THC from the oral route and oral doses are estimated from the information for Marinol®. A 10 mg b.i.d. dose of Marinol® (20 mg total per day) yielded a mean peak plasma THC concentration of 7.88 ng/mL (53). By comparison, consumption of a chocolate cookie containing 20 mg THC resulted in peak plasma THC concentrations ranging from 4.4 to 11 ng/mL, with a bioavailability of 6% (46). Tea prepared from *Cannabis* flowering tops and leaves has been documented but no data is available regarding efficacy (52).

3.3 Buccal
Dosing with Sativex® is described in the product monograph along with a titration method for proper treatment initiation (55).

3.4 Vaporization
The Dutch Office of Medicinal Cannabis has published "rough" guidelines on the use of vaporizers (52). Although the amount of cannabis used per day needs to be determined on an individual basis, the initial dosage should be low and may be increased slowly as symptoms indicate. The amount of cannabis to be placed in the vaporizer may vary depending on the type of vaporizer used. Studies using the Volcano® vaporizer have reported using up to 1 gram of dried cannabis in the chamber but 50 to 500 mg of plant material is typically used (50); THC concentrations up to 6.8% have been tested (43,50). Subjects appeared to self-titrate their intake in accordance with the THC content of the cannabis (43). The levels of cannabinoids released into the vapour phase increased with the temperature of vaporization (50). Vaporization temperature is typically between 180-195°C (52); higher temperatures (230°C) greatly increase the amounts of cannabinoids released but also increase the amounts of by-products (50).

4.0 Purported Indications and Clinical Use
The oral form of synthetic THC, dronabinol (2.5, 5 or 10 mg, dissolved in sesame oil) in capsules is marketed in the US and Canada as Marinol®. It is indicated for the treatment of severe nausea and vomiting associated with cancer chemotherapy and for AIDS- related anorexia associated with weight loss (53).

Sativex®, a buccal spray containing Δ^9 -THC 27 mg/mL and CBD 25 mg/mL is marketed (with conditions) in Canada as an adjunctive treatment for the symptomatic relief of neuropathic pain in adults with multiple sclerosis and as an adjunctive analgesic in adult patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain (55).

While there are many anecdotal reports of the therapeutic value of smoked marihuana, scientific studies supporting the safety and efficacy of marihuana for therapeutic claims are generally inconclusive. The existing scientific evidence for cannabinoids in treating various symptoms is summarized in the following sections.

4.1 Nausea and vomiting
Chemotherapy-induced nausea and vomiting (CINV) is one of the most distressing and common adverse events associated with cancer treatment (108). Patient claims that smoked cannabis relieves CINV are widely recognized. Cannabinoid CB_1 and CB_2 receptors have been found in areas of the brainstem associated with emetogenic control (109,110) and results from animal studies suggest the anti-emetic properties of cannabinoids are most likely related to their agonistic actions at CB_1 receptors (111,112). However, an *in vitro* study has shown that THC also antagonizes the 5-HT_3 receptor (113) raising the possibility that cannabinoids may exert their anti-emetic action through more than one mechanism. The evidence for cannabinoids such as nabilone (Cesamet®), dronabinol and levonantradol in treating CINV has been reviewed (114,115). While cannabinoids present clear advantages over placebo in the control of CINV, the evidence from randomized trials shows cannabinoids to be clinically only slightly better than conventional dopamine D2-receptor antagonist anti-emetics (114,115). In some cases, patients appeared to prefer the cannabinoids over these conventional therapies despite the increased incidence of adverse effects such as drowsiness, dizziness, dysphoria, depression, hallucinations, paranoia, and arterial hypotension. For certain patients, a degree of sedation and euphoria may be perceived as beneficial during chemotherapy. No clinical trials directly comparing cannabinoids to newer anti-emetics such as 5-HT_3 (Ondansetron, Granisetron) or NK-1 receptor antagonists have been reported to date (115,108). The use of cannabinoids (whether administered orally or by smoking) is currently considered a fourth-line adjunctive therapy in CINV when conventional anti-emetic therapies have failed (116,117,118,119,120,121). Few studies on the effects of combining cannabinoids and 5-HT_3 antagonists to treat

CINV exist. In one clinical study with a small sample size, the combination of dronabinol and ondansetron did not provide added benefit beyond that observed with either agent alone (122). However, an animal study showed that low doses of THC when combined with low doses of the 5-HT_3 receptor antagonist tropisetron were more efficacious in reducing emesis frequency than when administered individually (123). More research is required to determine if combination therapy provides added benefits above those observed with newer standard treatments.

4.2 Wasting syndrome (cachexia, *e.g.*, from tissue injury by infection or tumor) and loss of appetite (anorexia) in AIDS and cancer patients

4.2.1 To stimulate appetite and produce weight gain in AIDS patients

The ability of cannabis to increase appetite has been recognized anecdotally for many years (124). Results from epidemiological studies suggest that people actively using marihuana have higher intakes of energy and nutrients than non-users (125). Controlled laboratory studies with healthy subjects suggest exposure to marihuana whether by inhalation or oral ingestion of THC-containing capsules, correlates positively with an increase in food consumption, caloric intake and body weight (126,124). Studies showing a high concentration of CB_1 receptors in brain areas associated with control of food intake and satiety lend further support to the link between cannabis consumption and appetite regulation (127,128,129). Increasing evidence also suggests a role for the endocannabinoid system in modulating appetite, food intake and energy metabolism (reviewed in (128,129)).

The ability of marihuana to stimulate appetite and food intake has been applied to clinical situations where weight gain is deemed beneficial such as in HIV-associated muscle wasting and weight loss. One study showed that experienced HIV+ marihuana smokers with clinically significant muscle mass loss benefited from both dronabinol (4-8 times the standard 2.5 mg b.i.d dose or 10-20 mg daily) and smoked marihuana (3 puffs at 40 sec intervals, 1.3-3.9% THC). Both drugs produced substantial and comparable increases in food intake and body weight, as well as improvements in mood and sleep (130,131). The marihuana-associated increase in body weight appeared to result from an increase in body fat rather than lean muscle mass (132,133).

Oral synthetic THC, dronabinol, administered as capsules (Marinol®) is an approved indication in Canada for AIDS-related anorexia associated with weight loss. The Marinol® product monograph summarizes a randomized double-blind, placebo controlled-trial in 139 patients with the 72 patients in the treatment group initially receiving 2.5 mg dronabinol twice a day, then reducing the dose to 2.5 mg at bedtime due to side effects (feeling high, dizziness, confusion and somnolence) (134). Over the six week treatment period dronabinol significantly increased appetite, with a trend towards improved body-weight, and mood, and a decrease in nausea. At the end of the six week period, patients were allowed to continue receiving dronabinol, during which appetite continued to improve (135). This open-label, 12 month follow-up study suggested that dronabinol was safe and effective for long-term use for the treatment of anorexia associated with weight loss in patients with AIDS (135).

4.2.2 To stimulate appetite and produce weight gain in cancer patients

Anorexia is ranked as one of the more troublesome symptoms associated with cancer, with more than half of patients with advanced cancer experiencing a lack of appetite and/or weight loss (136,137). While it is anecdotally known that smoking marihuana can stimulate appetite, the effects of smoking marihuana on appetite and weight gain in patients with cancer cachexia have not been studied. The results from trials with oral THC (dronabinol) or oral cannabis extract are mixed and the effects, if any, appear to be modest. In two early studies, oral THC (dronabinol) improved appetite and food intake in some patients undergoing cancer chemotherapy (138,139). An open-label study of dronabinol (2.5 mg, 2-3 times daily, 4-6 weeks) in patients with unresectable or advanced cancer reported increases in appetite and food intake, but weight gain was only achieved in a few patients (140,141,142). Modest weight gain was obtained with a larger dose regimen of dronabinol (5 mg, 3 times daily), but the central nervous system side effects including dizziness and somnolence were limiting factors (143). In contrast, a randomized, double-blind placebo-controlled study involving cancer patients with related anorexia-cachexia syndrome failed to demonstrate any differences in patients' appetite across treatment categories (oral cannabis extract, THC or placebo) (144). Furthermore, when compared to megestrol acetate, an orexigenic medication, dronabinol was significantly ($p < 0.001$) less efficacious in reported appetite improvement and weight gain (145). According to a recent review of the medical management of cancer cachexia, the current level of evidence for cannabinoids such as dronabinol in the treatment of this condition is low (146). Cancer cachexia is not an approved indication for dronabinol either in Canada or the U.S.

4.2.3 Anorexia nervosa

The endocannabinoid system has been implicated in appetite regulation and is suspected to play a role in eating disorders such as anorexia nervosa (147,128). However, genetic studies have failed to agree on an association between genes coding for endocannabinoid system proteins and anorexia nervosa in spite of epidemiological and familial studies which suggest a genetic basis for this disorder (148,149). Little information exists on the use of marihuana to treat anorexia nervosa. No studies have looked at the effects of smoking marihuana and a randomized trial of oral THC failed to demonstrate weight gain in anorexic patients (150). Furthermore, three of the eleven patients administered THC also reported severe dysphoric reactions. Both the British Medical Association (2) and the Institute of Medicine (116) concluded that marihuana was unlikely to be effective in this group of patients.

4.3 Multiple sclerosis, amyotrophic lateral sclerosis, spinal cord injury

Anecdotal reports suggest marihuana can ameliorate spasticity in patients suffering from multiple sclerosis (MS) or spinal cord injury when other drugs fail or produce unacceptable side effects (2,151,116).

4.3.1 Multiple sclerosis

In humans, published reports spanning one hundred years suggest that people with spasticity may experience relief with cannabis (152). In the UK, 43% of patients with MS reported having experimented with cannabis at some point and 68% of this population used it to alleviate the symptoms of MS (153). In Canada, the prevalence of medicinal use of cannabis among patients seeking treatment for MS in 2000 was reported to be 16% in Alberta, with 43% stating they had used cannabis at some point in their lives (154). Fourteen percent of people with MS surveyed in 2002 in Nova Scotia reported using cannabis for medical purposes, with 36% ever having used cannabis for any purpose (106). MS patients reported using cannabis to manage symptoms such as spasticity and chronic pain as well as anxiety and/or depression (154,106). Patients also reported improvements in sleep. Reputed dosages of smoked cannabis by these patients varied from a few puffs to 1 gram or more at a time (106).

The results of randomized, placebo controlled trials with cannabinoids for the treatment of muscle spasticity are encouraging but modest. The large multicentre randomized placebo-controlled CAMS (Cannabis in Multiple Sclerosis) study researching the effect of cannabinoids for the treatment of spasticity and other symptoms related to MS enrolled over 600 patients (155). The primary outcome was change in overall spasticity scores using the Ashworth scale. The study did not show any statistically significant improvement in the Ashworth score in patients on oral cannabis extract or oral THC. However, there was evidence of a treatment effect on patient-reported spasticity and pain ($p=0.003$), with improvement in spasticity using either cannabis extract (61%) or THC (60%) compared to placebo (46%). Other randomized clinical trials on Sativex® (156,157) and standardized cannabis extract capsules (158) reported similar results, in that improvements were only seen in patient reports but not with objective measures. Spasticity is a complex phenomenon (159), is inherently difficult to measure and has no single defining feature (157). Furthermore, the reliability and sensitivity of the Ashworth scale has been called into question (155,157). Nevertheless, a long-term (12 months) follow-up to the CAMS study showed evidence of a small treatment effect of oral THC on muscle spasticity measured by objective methods (160). However, the clinical significance of this change from the patient perspective remained uncertain. A long-term, open-label, follow-up study of Sativex® concluded that the beneficial effect was maintained in patients who had initially benefited from the drug (161). In summary, although the subjective experience of symptom reduction was generally found to be significant, objective measures of spasticity did not reach statistical significance in the majority of clinical studies.

Generally speaking, orally administered cannabinoids are well tolerated (162,158,163). Clinical trials to date do not indicate serious adverse effects associated with the use of cannabis-based medicinal extracts to treat MS-related symptoms. However, information is lacking regarding the long-term adverse effects of cannabinoid use. The most commonly reported physical adverse effects are dizziness, drowsiness and dry mouth (155,163). A more recent study concluded that Sativex® treatment in cannabis-naïve MS patients was not associated with cognitive impairment (163). However, the study did raise the possibility that higher dosages could precipitate changes in psychological disposition, especially in those patients with a prior history of psychosis.

4.3.2 Amyotrophic lateral sclerosis

The endocannabinoid system has been implicated in the pathogenesis of amyotrophic lateral sclerosis (ALS) and under certain conditions, cannabinoids have been reported to delay disease progression and prolong survival in mouse models of ALS (reviewed in (164)). Anecdotal reports suggest decreased muscle cramps and fasciculations in ALS patients who smoke herbal cannabis or drink cannabis tea with up to 10% of these patients using cannabis for symptom control (165). Few clinical trials of cannabis for the treatment of symptoms associated with ALS exist and the results of the studies are mixed. In one 4-week, randomized, double-blind, cross-over pilot study of 19 ALS patients, 2.5-10 mg per day of dronabinol were associated with improvements in sleep and appetite but not cramps or fasciculations (166). In contrast, a shorter (2-week) study reported no improvement in these measures in ALS patients taking 10 mg per day of dronabinol (165). In either case, dronabinol was well tolerated with few side effects.

4.3.3 Spinal cord injury

Limited information exists regarding the use of cannabinoids to treat symptoms associated with spinal cord injury (SCI) such as pain, spasticity, muscle spasms, urinary incontinence and difficulties sleeping. No clinical trials of smoked marihuana for the treatment of these symptoms have been documented, but subjective improvements have been reported by patients smoking marihuana (167,116). Double-blind, cross-over, placebo-controlled studies of oral THC and/or THC:CBD extract (Sativex®) suggested modest improvements in pain, spasticity, muscle spasms and sleep quality in patients with SCI (168,116,169). A randomized, double-blind, placebo-controlled parallel study using a minimum of 15-20 mg THC/day (mean daily doses of 31 mg THC orally or 43 mg THC-hemisuccinate rectally) showed a statistically significant improvement in spasticity scores in patients with SCI (170). A more recent double-blind, placebo-controlled, cross-over study using nabilone (0.5 mg b.i.d.) also showed an improvement in spasticity compared to placebo in patients with SCI (171).

4.4 Epilepsy

In vitro studies as well as those carried out in animals generally suggest an anti-convulsant role for cannabinoids (172,173,174,175) however a pro-convulsant role has also been described (176). CB_1 receptors are located mainly presynaptically where they typically inhibit the release of classical neurotransmitters (177). The purported anti-epileptic effect of cannabinoids is thought to be mediated by CB_1-receptor dependent presynaptic inhibition of glutamate release (178); epileptogenic effects may be triggered by presynaptic inhibition of GABA release (179,172,173,180,175). CB_1 receptor agonists therefore have the potential to trigger or suppress epileptiform activity depending upon which cannabinoid-sensitive presynaptic terminals are preferentially affected (i.e. glutamatergic or GABAergic) (178).

Increasing evidence points to a role for the endocannabinoid system in the modulation of neuronal tone and excitability. Human and animal studies suggest epileptic activity is associated with changes in the levels and distribution of CB_1 receptors in the hippocampus (181,182,183) and reduced levels of the endocannabinoid anandamide have been detected in the cerebrospinal fluid of patients with untreated newly diagnosed temporal lobe epilepsy (184). These and other studies suggest dysregulation of the endocannabinoid system may play a role in epileptogenesis and could represent a target for anti-epileptic therapies. However, a review of the literature describing the effects of marihuana on epileptic symptoms in humans concluded that although cannabis use can reduce seizure frequency in some cases and provoke seizures in others, in the majority of cases it probably has no effect (185). This may be caused by the rather unspecific actions of exogenously administered cannabinoids such as THC which would target both excitatory and inhibitory neurons. Cannabidiol (CBD) has also been examined as a potential anti-epileptic in humans (see (186) for full review) but these early studies have not been followed up with larger and more convincing clinical trials.

4.5 Pain

4.5.1 Cancer pain

There are few properly controlled clinical trials of smoked marihuana for the treatment of cancer pain. Two randomized, double-blind, placebo-controlled studies suggested oral THC (dronabinol, Marinol®) provided an analgesic effect in patients suffering from moderate to severe continuous pain due to advanced cancer. The first (187) was a dose ranging study of 5, 10, 15 and 20 mg THC, given in successive days, to ten cancer patients. Significant pain relief was found at the 15 and 20 mg dose levels, but at these higher doses patients were heavily sedated and mental clouding was common. A second, placebo-controlled study (188) compared 10 and 20 mg oral

THC with 60 and 120 mg codeine in 36 patients with cancer pain. While the lower and higher doses of THC were equianalgesic to the lower and higher doses of codeine respectively, statistically significant differences in analgesia were only obtained between placebo and 20 mg THC and between placebo and 120 mg codeine. The 10 mg THC dose was well tolerated and, despite its sedative effect, appeared to have mild analgesic potential. The 20 mg THC dose induced somnolence, dizziness, ataxia, and blurred vision. Extreme anxiety was also observed at this dose in a number of patients. This side effect profile is supported by a report concerning a synthetic analogue of THC also tested in controlled trials (189). While it was equivalent in efficacy to codeine, it was not considered clinically useful because of the frequency of side effects. A recent randomized, double-blind, placebo-controlled, parallel-group trial of patients suffering from intractable cancer-related pain suggested that an orally administered THC:CBD extract containing 2.7 mg of THC and 2.5 mg CBD per dose (Sativex®) is an efficacious adjunctive treatment for pain not fully relieved by strong opioids (190). 43% of patients taking the extract achieved a 30% or greater improvement in their pain score which was twice the number of patients who achieved this response in the THC and placebo groups. Both the THC:CBD and the THC medications were well tolerated and adverse events were similar to those seen in other THC:CBD clinical trials (somnolence, dizziness, and nausea).

In Canada, Sativex® is approved (with conditions) as an adjunctive analgesic in cancer pain (55). It is indicated as an adjunctive analgesic treatment in adults with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent pain.

4.5.2 Non-cancer pain

Chronic, non-cancer pain is a complex syndrome that involves physical, psychological and psychosocial factors that contribute to a reduced quality of life (191). The anti-nociceptive efficacy of cannabinoids has been unequivocally demonstrated in several animal models of inflammatory and neuropathic pain (reviewed in (192)). Furthermore, animal studies have shown that cannabinergic modulation of neuronal circuits in the brain and spinal cord can inhibit nociceptive processing (193,194,195,196). More recent studies suggest that peripheral nociceptors also play a very important role in the modulation of cannabinoid-mediated analgesia (197). Less clear are the analgesic effects of smoked cannabis in experimentally-induced pain studies in human volunteers which have been inconclusive because of poor study design and conflicting results. Some studies on smoked cannabis report an analgesic effect (198,199) while a study on smoked cannabis (200) and one on oral cannabis (201) did not observe any analgesic effect. An experimental pain model applied to normal volunteers reports that oral THC and morphine provided synergistic analgesic effects (202). However, the authors caution that translating the results gathered from pain models and applying them in the clinic is not likely to be a straight forward process and that future studies should focus on clinical rather than experimental pain (202).

An off-label retrospective descriptive study of 20 adult patients suffering from chronic non-cancer pain of various etiologies reported subjective overall improvement and reduced pain intensity with nabilone as an adjunctive pain-relief therapy (191). Furthermore, beneficial effects on sleep and nausea were the main reasons for continuing use. A meta-analysis of all cannabinoid trials for analgesia concluded that as well as having effects on the CNS that limit their use, cannabinoids are no more effective than codeine as analgesics (203)

4.5.2.1 Postoperative pain

To date, there are only four published reports on the use of cannabis in postoperative pain (204,205,206,207). The conclusions from these studies were that cannabinoids are not ideally suited to manage postoperative pain, being either moderately effective (204,207), not different from placebo (205), or even antianalgesic at high doses (206). However, a definitive conclusion on the role of cannabinoids in the postoperative setting cannot yet be made because of the different drugs, dosages, routes of administration and protocols that were used in these studies (208).

4.5.2.2 Neuropathic pain

Cannabinoids suppress hyperalgesia and allodynia induced by diverse neuropathic states through CB_1 and CB_2-specific mechanisms (209). Short-term clinical studies suggest cannabinoids are moderately effective in reducing intractable central or peripheral neuropathic pain of various etiologies in individuals already receiving analgesic drugs (210). Side effects appear to be comparable to existing treatments and include dizziness, ataxia, a feeling of intoxication, xerostomia, dysgeusia, sedation and hunger (211). These effects may be minimized by employing low doses that are gradually escalated. The Canadian Pain Society considers cannabis-based therapies (dronabinol and Sativex®) to be fourth-line treatments for neuropathic pain, mostly as

adjuvant analgesics for pain conditions refractory to standard drugs (212). Health Canada has approved Sativex® (with conditions) as an adjunct treatment for the symptomatic relief of neuropathic pain in multiple sclerosis (MS) (55).

In one randomized controlled trial (RCT) using smoked cannabis, significant decreases in central and peripheral neuropathic pain that generally followed a linear dose-response relationship were reported (213). In another study, a greater than 30% decrease in HIV-associated sensory neuropathic pain was reported in 52% of patients smoking cannabis (3 times daily) compared to 24% in the placebo group (214). The number needed to treat (NNT) for 30% reduction in pain was 3.6 and was comparable to that reported for other analgesics in the treatment of chronic neuropathic pain. Yet another study showed a 30% decrease in HIV-associated distal sensory predominant polyneuropathic pain in 46% of patients smoking cannabis (1-8% Δ^9-THC, four times daily) compared to 18% in the placebo group (215). The NNT in this study was 3.5. Cognitive changes appeared to be more pronounced with higher doses of Δ^9-THC (213). More recently, an RCT of smoked cannabis for neuropathic pain caused by trauma or surgery and refractory to conventional therapies showed that compared to placebo, smoking 25 mg of cannabis containing 9.4% THC three times per day was associated with a modest but statistically significant decrease in average daily pain intensity (105). In addition, there were statistically significant improvements in measures of sleep quality and anxiety.

An RCT of patients suffering from MS-associated central neuropathic pain reported a decrease in central pain with daily doses of dronabinol (10 mg) (216). The number needed to treat for 50% pain reduction was 3.5. 54% of patients had a ≥33% reduction in pain during dronabinol treatment compared with 21% of patients during placebo. The pain reduction in this study was comparable to that seen with other drugs commonly used in the treatment of neuropathic pain conditions (216).

A number of randomized, placebo-controlled, double-blind crossover and parallel studies have shown a significant reduction in central or peripheral neuropathic pain of various etiologies following treatment with Sativex® (217,218,219). In all three studies, patients were concomitantly using other analgesic drugs. The NNT for 30% pain reduction (deemed clinically significant) varied between 8 and 9 whereas the NNT for 50% pain reduction for central neuropathic pain was 3.7 and peripheral pain was 8.5.

While cannabidiol (CBD) was found to be an effective oral analgesic when administered chronically in a rat pain model (220), a study of oral CBD in 10 patients with chronic neuropathic pain found no significant pain relief (221).

4.5.2.3 Rheumatoid arthritis

A functional endocannabinoid system has been identified in the knee synovia of patients with end-stage osteoarthritis and rheumatoid arthritis (RA) (222). Furthermore, the levels of anandamide (AEA) and 2-arachidonoylglycerol (2-AG) in the synovial fluid of patients with arthritis were increased compared to non-inflamed normal controls, although the significance of these findings is unclear (222). A preliminary study assessing the effectiveness of Sativex® in pain caused by rheumatoid arthritis, (223) reported a modest but statistically significant analgesic effect on movement and at rest, as well as on quality of sleep. Administration of Sativex® was well tolerated and no significant toxicity was observed. The mean daily dose in the final treatment week was 5.4 pump actuations (equivalent to 14.6 mg THC and 13.5 mg CBD) (223). Although the differences observed were small and variable across the participants, the results indicated a therapeutic potential for cannabinoids in RA and further research was suggested.

4.5.2.4 Headache

Historical and anecdotal evidence suggests a role for cannabinoids in the treatment of headache (224). Endocannabinoid deficiency has been postulated to underlie the pathophysiology of migraine (225). The concentrations of AEA are decreased in the cerebrospinal fluid of migraineurs, while the levels of calcitonin-gene-related-peptide (CGRP) and nitrous oxide (NO), normally inhibited by AEA and implicated in triggering migraine, are increased (226,227). In addition, the activity of AEA-degrading enzymes is significantly decreased in chronic migraineurs compared to controls (228). This drop in activity could represent a compensatory mechanism meant to elevate the low levels of AEA in migraine sufferers. Few, if any, clinical studies of cannabinoids to treat headache

exist. In one case report, a patient suffering from pseudotumour cerebri and chronic headache reported significant pain relief after smoking marihuana (229). In another case report, a patient complaining of cluster headaches refractory to multiple acute and preventive medications also reported dramatic improvement from smoking marihuana or taking dronabinol (5 mg) (230). These single-patient case-studies should be interpreted with caution and it should also be noted that marihuana use has been associated with reversible cerebral vasoconstriction syndrome and severe headache (231). In addition, headache is one of the most frequently reported physical symptoms associated with cannabis withdrawal (232). It is therefore possible that using marihuana simply relieves headache caused by marihuana withdrawal.

4.5.2.5 Fibromyalgia

A randomized, double-blind, placebo-controlled trial of nabilone 1 mg b.i.d. for the treatment of fibromyalgia showed statistically significant improvements in a subjective measure of pain relief and anxiety as well as on scores on the fibromyalgia impact questionnaire after 4 weeks of treatment (233). However, no significant changes in the number of tender points or tender point pain threshold were observed. Nabilone did not have any lasting benefit in subjects when treatment was discontinued.

4.6 Other diseases and symptoms

4.6.1 Movement disorders

The individual components of the endocannabinoid system (ligands, receptors, synthesizing and degrading enzymes) are particularly abundant in areas of the brain which control movement, such as the basal ganglia (234). Motor effects generally arise as a consequence of changes in endocannabinoid system activity with activation of the CB_1 receptor typically resulting in inhibition of movement (234). A number of studies have reported changes in CB_1 receptor levels and CB_1 receptor activity in motor diseases such as Parkinson's and Huntington's disease (235,236,237,238) and suggest a role for the endocannabinoid system in the pathology of these and other neurological diseases.

4.6.1.1 Dystonia

Anecdotal reports suggest cannabis might alleviate symptoms associated with dystonia (239); however no controlled studies of smoked marihuana in dystonic patients have been published. A six-week, open-label, pilot trial of five patients taking 100-600 mg/day of cannabidiol (CBD) reported modest dose-related improvements in all subjects but a worsening of tremor and hypokinesia in 2 patients with co-existing Parkinson's disease (240). Results of a double-blind, randomized, placebo- controlled study of 15 patients taking a single 0.03 mg/kg dose of nabilone showed no significant reduction in dystonia (241).

4.6.1.2 Huntington's disease

The relationship between the endocannabinoid system and Huntington's disease (HD) has been reviewed (242). Results from studies in animal models of HD as well as post-mortem studies in HD patients indicate downregulation and desensitization of CB_1 receptors in the brain (243,235,244,245,246,247). These findings suggest hypofunctionality of the endocannabinoid system may contribute to the pathophysiology of HD. This, together with the well-known protective properties of cannabinoid-related compounds, suggests that cannabinoids might help delay or arrest the development of the disease (242). However, there is little clinical evidence to support a role for cannabinoids in the treatment of HD, mostly because so few clinical trials have been carried out. In one double-blind, placebo-controlled, 15-week, cross-over trial of 15 patients with HD (248), 10 mg/kg/day of oral CBD did not improve the symptoms associated with HD. One randomized, double-blind, placebo-controlled, cross-over pilot study found little or no beneficial effect of nabilone over placebo in patients with HD (249). However, nabilone was well-tolerated and did not appear to exacerbate chorea or HD-associated psychosis, although some adverse effects such as drowsiness and forgetfulness were noted. The results from single-patient case studies are mixed. In one study, 1.5 mg nabilone increased choreatic movements (250), while in another case improved mood and decreased chorea was noted in a patient who had smoked cannabis and then continued on 1 mg nabilone b.i.d. (251).

4.6.1.3 Parkinson's disease

The role of cannabinoids in Parkinson's disease (PD) is complex. Endocannabinoid ligands, their synthesizing and degrading enzymes, and cannabinoid-activated receptors are highly abundant in the basal ganglia, the brain structures primarily affected in PD (234). While the levels of CB_1 receptors appear to be downregulated during the early, presymptomatic stages in a number of animal models of PD, increased CB_1 receptor density and function and elevated endocannabinoid levels are observed during the intermediate and advanced phases of the disease (237,252,253). These changes along with other factors such as the complex distribution of cannabinoid receptors within the basal ganglia may explain the paradoxical effects of cannabinoids in PD. Results from animal studies suggest cannabinoid receptor agonists induce hypokinesia and thus are unlikely to be a suitable first-line treatment for PD (254,234). On the other hand, cannabinoid-induced hypokinesia could be useful in attenuating the dyskinesia observed in PD patients on long-term levodopa treatment (254). Consistent with the complex pharmacology of cannabinoid receptors in the basal ganglia, the results of clinical trials examining the role of cannabinoids in the treatment of PD are mixed. One study involving five patients suffering from idiopathic PD found no improvement in tremor after smoking marihuana (1 g cigarettes containing 2.9% THC), whereas all subjects benefited from the administration of levodopa and apomorphine (255). A small randomized clinical trial of the synthetic cannabinoid nabilone in seven patients with PD found that the treatment reduced levodopa-induced dyskinesia (256). In contrast, a randomized double-blind crossover study demonstrated that oral cannabis extract did not produce any pro- or anti-parkinsonian action (257). Given the current state of knowledge, the benefits of using cannabinoids in the treatment of PD remain unestablished and further research is required.

4.6.1.4 Tourette's syndrome

Anecdotal reports have suggested amelioration of symptoms associated with Tourette's syndrome (TS) when smoking marihuana (258,259). A randomized, double-blind, placebo- controlled crossover trial of single oral doses of THC (5, 7.5 or 10 mg) in 12 adult patients with TS showed plasma concentration-related improvements in control of motor and vocal tics and obsessive-compulsive behaviour, with no serious side-effects; although transient, mild side-effects (headache, nausea, ataxia, fatigue, anxiety) were noted in five patients (260). In contrast to healthy marihuana users, neither a 5 mg nor a 10 mg dose of THC caused cognitive impairment (260).This study was followed up by a 6-week randomized, double-blind, placebo- controlled follow-up trial by the same group; they reported a significant difference in tic reduction compared to placebo in some patients and no detrimental effects on neuropsychological performance during or after treatment with 10 mg doses of THC (261). The major limitations of all three clinical studies were their small sample size and their relatively short duration. Therefore, although the results suggest THC benefits some patients suffering from TS, there is currently not enough evidence to fully support the use of cannabinoids in treating tics and obsessive-compulsive behaviour in people with TS (249).

4.6.2 Glaucoma

Glaucoma is a multifactorial disease characterized by the progressive degeneration of the optic nerve and the death of retinal ganglion cells (RGC) ultimately leading to irreversible blindness (262). Increased intraocular pressure (IOP) has been implicated in the pathophysiology of glaucoma, however inadequate blood supply to the optic nerve, oxidative damage, and apoptosis of RGCs are also contributing factors (263,264,262,265). Smoking or eating cannabis has been shown to reduce IOP (266,267,268) but these means of delivery have serious drawbacks including short duration of cannabinoid action (3-4 h) and unwanted physical and psychotropic effects. An endocannabinoid system exists in a number of ocular tissues and post-mortem studies have detected decreased levels of endocannabinoids in such tissues taken from glaucoma patients (269). Ocular (as well as systemic) administration of cannabinoids typically lowers IOP by up to 30% (see (264) for a full reference list). How cannabinoids reduce IOP is unclear, but several possible mechanisms have been proposed including reduction of capillary pressure, decreased aqueous humour production and improved aqueous humour uveoscleral outflow and outflow facility (270,271,272,273,274). A well-controlled pilot study reported that sublingual doses of 5 mg THC significantly but temporarily reduced IOP, while 20 mg cannabidiol (CBD) had no effect and 40 mg of CBD caused a transient increase in IOP (275). A non-randomized, uncontrolled study reported some improvement in IOP in patients with end-stage, open-angle glaucoma taking oral THC (2.5 or 5 mg q.i.d. up to a maximum of 20 mg/day) however patients appeared to develop tolerance to the ocular effects of THC and almost half discontinued treatment due to THC-associated toxicity (276). Aside from lowering IOP, cannabinoids such as

THC and CBD may also have neuroprotective effects which could also be useful in the management of glaucoma (277,278,279,280,281,282,283,284,264,285,286). These benefits notwithstanding, neither the American Glaucoma Society nor the Canadian Ophthalmological Society recommend the use of cannabinoids for the treatment of glaucoma at this time due to the availability of other therapeutic options and the current inability to separate the potential clinical action of marihuana from its undesirable neuropsychological and behavioural effects (265,287).

4.6.3 Asthma

There is historical and anecdotal evidence for marihuana as a treatment for asthma (288). Clinical studies have demonstrated significant decreases in airway resistance and increases in specific airway conductance in healthy, habitual marihuana smokers shortly after smoking marihuana (289,290) and this effect has been largely attributed to the bronchodilatory properties of THC (291). For asthmatics, the benefits of smoking marihuana are likely to be minimal. While smoking marihuana appears to decrease bronchospasm, increase bronchodilation and modestly improve respiratory function in some asthmatics in the short-term (292,293,294), marihuana smoke contains noxious gases and particulates that irritate and damage the respiratory system (291); hence it is not a viable long-term therapy for asthma. Alternate methods of THC delivery by aerosol or oral administration have also been studied. 100 and 200 µg of aerosolized THC significantly improved ventilatory function in asthmatics and was generally well tolerated (295,296). In another study, 5-20 mg of aerosolized THC rapidly and effectively increased airway conductance in healthy subjects but caused either bronchodilation or bronchoconstriction in asthmatics (297). Oral administration of 10 mg THC or 2 mg nabilone did not produce clinically significant bronchodilation in patients with reversible airways obstruction (298,288,299). Although animal studies with classical and synthetic cannabinoids suggest a promising role for cannabinoid-based compounds in the treatment of asthma (300,301,302), cannabinoids are not currently indicated for this condition.

4.6.4 Hypertension

CB_1 receptors are expressed on various peripheral tissues including the heart and vasculature, and cannabinoid agonists and endocannabinoids decrease arterial blood pressure and cardiac contractility (reviewed in (303)). Very few studies on the effects of marihuana on hypertension exist. Inhalation of marihuana with 2.8% THC caused a greater and longer-lasting decrease of arterial blood pressure in hypertensive subjects compared to normotensives (304). In one case report, a woman with longstanding idiopathic intracranial hypertension reported improvement in her symptoms after smoking marihuana or treatment with dronabinol (10 mg b.i.d initially, then 5 mg b.i.d.). Although cannabinoids may have a role to play in attenuating hypertension, tolerance to the cardiovascular effects along with the well-known adverse physical and psychotropic effects would preclude their consideration as a long-term treatment in hypertension (2).

4.6.5 Psychiatric disorders

There are anecdotal and historical claims regarding the beneficial effects of cannabis in the treatment of anxiety, depression, and sleep disorders, as well as for the treatment of alcohol and opiate withdrawal symptoms (305). However, insufficient clinical evidence exists at this time to recommend the use of cannabinoids in the treatment of such disorders.

Results from animal studies suggest low doses of CB_1 receptor agonists or inhibitors of the enzyme fatty acid amide hydrolase (FAAH), which degrades anandamide, reduce anxiety-like behaviour and increase antidepressant-like responses. On the other hand, high-level stimulation of the CB_1 receptor or administration of CB_1 receptor antagonists elicit opposite responses (306,307,308,309). CB_1 receptor agonists and FAAH inhibitors appear to enhance central serotonergic and noradrenergic transmission similar to the actions of antidepressant medications (306,310).

Clinical trials of marihuana or oral THC to treat anxiety or depression show either a lack of improvement or worsening of the condition (311,312,313,314). More recently, a number of studies have suggested an association between cannabis use and the development of psychosis, especially in people susceptible to psychotic disorders as well as in adolescents (315,316,317,318,319). A population-based, 13-year longitudinal study has suggested an association between exposure to cannabis and protracted suicidal thoughts or attempts in young Norwegians (320). On the other hand, preliminary evidence suggests that cannabidiol (CBD) may have anti-psychotic (321) and anxiolytic (322) activity.

Anecdotal information and some animal studies suggest that cannabinoids may be useful in treating the symptoms associated with opiate withdrawal (323,324,325) but no clinical studies support this indication (2).

4.6.6 Alzheimer's disease and dementia

Although increasing evidence from pre-clinical and clinical studies suggests a potential therapeutic role for cannabinoids in Alzheimer's disease (AD), there is insufficient clinical evidence at this time to support the use of cannabinoids in this regard.

Results from *in vitro* studies suggest cannabinoids reduce the neurotoxic effects associated with the deposition of Aβ plaques (reviewed in (326)). One study performed in a rat model of AD suggested the synthetic cannabinoid WIN 55,212-2 could exert a neuroprotective function (327). A double-blind, placebo-controlled, 6-week crossover study of 12 patients suffering from Alzheimer-type dementia reported 5 mg of dronabinol daily was associated with a decrease in disturbed behaviour (328). Adverse reactions such as fatigue, somnolence and euphoria were reported in dronabinol-treated patients. One open-label pilot study of 6 patients suggested an evening dose of 2.5 mg dronabinol reduced nocturnal motor activity and agitation in those who were severely demented (329).

4.6.7 Inflammation

The ability of cannabinoids to suppress the production of pro-inflammatory cytokines and chemokines has been well-documented and may have therapeutic applications in diseases with an underlying inflammatory component (330,331).

4.6.7.1 Inflammatory bowel disease (Crohn's disease, colitis)

Although there are no reports of clinical trials of cannabinoids for the treatment of inflammatory bowel disease (IBD), anecdotal evidence suggests that patients suffering from IBD may experience symptomatic relief by smoking marihuana. Cannabinoid receptors are expressed in the enteric nervous system, in human colonic epithelium and in a number of colonic epithelial cell lines (332,333). Furthermore, cannabinoids appear to have many functions in the digestive system including regulating gastric acid production, gastrointestinal motility, secretion and ion transport, and visceral sensation and inflammation (reviewed in (334)). Intestinal biopsies taken from patients with IBD including ulcerative colitis, Crohn's disease, diverticulitis, and celiac disease show increased CB receptor expression and/or enhanced endocannabinoid levels (335,332,336,337). Pre-clinical experiments in animal models of IBD suggest cannabinoids and endocannabinoids may limit intestinal inflammation via activation of CB receptors (338,339,340,341,342,343). Although the results from such studies are encouraging, further research is required to determine if cannabinoids are beneficial in IBD patients.

4.6.7.2 Inflammatory skin diseases (dermatitis, psoriasis, pruritus)

The skin possesses an endocannabinoid system (ECS) (344). CB_1 and CB_2 receptors are expressed in a number of skin cells including epidermal keratinocytes, cutaneous nerves and nerve fibres, sebaceous cells, myoepithelial cells of eccrine sweat glands and sweat gland ducts, mast cells and macrophages (345). In addition, elements of the ECS have been detected in human epidermal keratinocytes (346). The ECS appears to regulate the balance between keratinocyte proliferation, differentiation and apoptosis; it may therefore play a role in cutaneous homeostasis and in diseases such as psoriasis, which is characterized by keratinocyte proliferation and inflammation (346,347,344).

The results from pre-clinical studies on the role of cannabinoids in the modulation of cutaneous allergic reactions are mixed. Some studies suggest a protective role for cannabinoids while others, an antagonistic one (reviewed in (344)). In clinical studies, experimentally-induced, histamine-triggered pruritus was reduced by peripheral administration of the cannabinoid receptor agonist HU210, and the accompanying increases in skin blood flow and neurogenic mediated flare responses were attenuated (348). In another study, topically applied HU210 significantly reduced the perception of pain in human subjects following administration of capsaicin and reduced heat hyperalgesia and touch-evoked allodynia without any psychomimetic effects (349). Thus, it is possible that cannabinoids have therapeutic value in the treatment of certain inflammatory skin conditions (such as psoriasis, pruritus, and dermatitis), but further research is required. On the other

hand, there have also been some case reports of contact urticaria following exposure to cannabis flowers, and extreme sensitization to THC and cannabinol has also been documented in an animal model of contact dermatitis (350,351).

4.6.8 Bladder dysfunction

Bladder dysfunction occurs in most patients suffering from multiple sclerosis (MS) or spinal cord injury (352). The most common complaints are increased urinary frequency, urgency, urge and reflex incontinence (353). Cannabinoid receptors are expressed in human bladder detrusor and urothelium (354,355) and may help regulate detrusor tone and bladder contraction as well as affecting bladder nociceptive response pathways (reviewed in (355)).

A survey of MS patients regularly using cannabis for symptomatic relief of urinary problems reported that over half claimed improvement in urinary urgency (356). A 16-week, open-label pilot study of cannabis-based extracts (Sativex® followed by 2.5 mg THC only) for bladder dysfunction in 15 patients with advanced MS showed significant decreases in urinary urgency, number and volume of incontinence episodes, frequency and nocturia (357). Improvements were also noted in patient self-assessments of pain and quality of sleep. A subsequent randomized controlled trial of 250 MS patients suggested a clinical effect of orally administered cannabis (2.5 mg THC or 1.25 mg cannabidiol (CBD) with <5% other cannabinoids per capsule up to a maximum 25 mg/day) on incontinence episodes (352).

4.6.9 Anti-neoplastic properties

Results from *in vitro* and animal studies suggest cannabinoids and endocannabinoids inhibit tumour growth and the progression of several types of cancer including glioma, glioblastoma multiforme, breast, prostate, thyroid, colon carcinoma, leukemia, and lymphoid tumours (reviewed in (358,359)). Cannabinoid agonists appear to have a bi-modal mechanism of action with low concentrations being pro-proliferative and high concentrations having anti-proliferative effects (358).

There is only one report of a clinical study of THC to treat cancer (360). In this pilot study, nine patients with glioblastoma multiforme who had failed standard surgical and radiation therapy, had clear evidence of tumour progression, and had a minimum Karnofsky score of 60 were treated with 20-40 µg THC intracranially per day (with doses up to 80-180 µg per day). Median treatment duration was 15 days (360). While intracranial administration of THC appeared to be well tolerated, the effect of THC on patient survival was unclear. Nevertheless, *in vitro*, THC inhibited the proliferation and decreased the viability of tumour cells isolated from glioblastoma biopsies most likely through a combination of cell-cycle arrest and apoptosis (360,359). A more recent *in vitro* study suggests that CBD enhances the inhibitory effects of THC on human glioblastoma cell proliferation and survival (359).

5.0 Contraindications

The contraindications that apply to those considering using Sativex® or Marinol® also apply to the use of marihuana. Marihuana is contraindicated in any person under the age of 18 as well as any patient who has a history of hypersensitivity to any cannabinoid or to smoking. Marihuana should not be used in patients with liver, kidney or cardio-pulmonary disease, or a history of psychiatric disorders, particularly schizophrenia. It is also contraindicated in women of childbearing age not on a reliable contraceptive, as well as those planning pregnancy, those who are pregnant or women who are breastfeeding. Men intending to start a family are also discouraged from using marihuana. Marihuana may also exacerbate the CNS depressant effects of sedatives, including alcohol. Concomitant use of marihuana with other drugs may increase the incidence of adverse effects (see section 7.3).

6.0 Warnings

The dose of marihuana to be smoked is difficult to estimate and is affected by the source of the plant material, its processing and by different smoking techniques. These include depth of inhalation and breath-holding and the number and frequency of puffs as well as how much of the cigarette is smoked. Smoking should be gradual and should cease if the patient begins to experience the following effects: disorientation, dizziness, ataxia, agitation, anxiety, tachycardia and orthostatic hypotension, depression, hallucinations, psychosis.

Marihuana is one of the most widely abused illicit drugs, can produce physical dependence and has the potential to be addictive (361,362). The drug has complex effects in the CNS and can cause cognitive and memory impairment, changes in mood, altered perception and decreased impulse control (363,364,365,366). Patients should be supervised when administration is initiated.

Any patient experiencing a psychotic reaction to marihuana should stop taking the drug immediately and be kept under observation until the normal mental state is regained.

Occupational hazards: Patients using marihuana should be warned not to drive or perform hazardous tasks such as operating heavy machinery because impairment of mental alertness and physical coordination may decrease their ability to perform such tasks (367). Such impairment can last for over 24 h after last use because of the long half-life of THC.

Pregnancy: Use of marihuana during pregnancy should be avoided as there is some evidence of long-term developmental problems in children exposed to marihuana *in utero* (368,369).

Lactation: Cannabinoids are excreted in human milk and may be absorbed by the nursing baby (370,371). Because of potential risks to the child, nursing mothers should not use marihuana.

7.0 Precautions

7.1 General

The risk/benefit ratio of marihuana should be carefully evaluated in patients with the following medical conditions, because of individual variation in response and tolerance to its effects as well as the difficulty in dosing noted in section 3.0:

- Marihuana should be used with caution in patients with cardiac disorders because of occasional hypotension, possible hypertension, syncope, or tachycardia.
- Smoked marihuana is not recommended in patients with respiratory insufficiency such as asthma or chronic obstructive pulmonary disease.
- Marihuana should be used with caution in patients with a history of substance abuse, including alcohol abuse, because they may be more prone to abuse marihuana, which itself, is a frequently abused substance.
- Patients with mania, depression, or schizophrenia should be under careful psychiatric monitoring if marihuana is taken, because it may exacerbate these illnesses.
- Marihuana should be used with caution in patients receiving concomitant therapy with sedatives, hypnotics or other psychoactive drugs because of the potential for additive or synergistic CNS effects.
- Patients should be advised of the negative effects on memory and to report any mental or behavioural changes that occur after using marihuana.
- Patients with ongoing chronic hepatitis C should be strongly advised to abstain from daily cannabis use, as this has been shown to be a predictor of steatosis severity in these individuals (372).

7.2 Dependence and withdrawal

Tolerance, psychological and physical dependence can occur with prolonged use of marihuana (27,373). Tolerance to cardiovascular effects occurs quickly, but the dependence is slower to develop and appears more likely with higher, more frequent dosing (374,375).

7.3 Drug interactions

The most clinically significant interaction may occur when cannabis is taken with other CNS depressant drugs such as sedative-hypnotics or alcohol. Some studies have reported enhanced CNS depressant effects when marihuana and alcohol are used in combination (376,377).

Substances that inhibit CYP isoenzymes 2C9 and 3A4 such as macrolides (clarithromycin and erythromycin), antimycotics (itraconazole, fluconazole, ketoconazole, miconazole), calcium antagonists (diltiazem, verapamil), HIV protease inhibitors (ritonavir), amiodarone and isoniazid can increase the bioavailability of THC as well as the chance of experiencing THC-related side-effects (52). Drugs that accelerate THC metabolism via 2C9 and 3A4 isozymes such as rifampicin, carbamazepine, phenobarbital, phenytoin, primidone, rifabutin, troglitazone, and Saint John's Wort may conversely decrease the bioavailability of THC and hence, its effectiveness if used in a therapeutic context (52). THC,

CBD, and CBN inhibit CYP isozymes such as CYP1A1, 1A2 and 1B1 (83). Cannabis may therefore increase the bioavailability of drugs metabolized by these enzymes. Such drugs include amitryptiline, phenacetin, theophylline, granisetron, dacarbazine, and flutamide (83). Patients taking fentanyl (or related opioids) and antipsychotic medications (clozapine or olanzapine) may also be at risk of experiencing adverse effects (86,85,87). Clinicians should therefore be aware of other medications that the patient is taking and carefully monitor patients using these drugs along with cannabis or cannabinoids.

7.4 Drug screening tests

Because of the long half-life of elimination of cannabinoids and their metabolites, drug tests screening for cannabinoids can be positive weeks after last marihuana use (378,379).

8.0 Adverse Effects

8.1 Carcinogenesis and mutagenesis

While there are many cellular and molecular studies that provide strong evidence that smoked marihuana is carcinogenic (reviewed in (27)), the epidemiological evidence of a link between marihuana use and cancer is still inconclusive. One epidemiological study in relatively young health maintenance organization (HMO) clients found an increased number of men with prostate cancer in those who smoked cannabis and other non-tobacco materials (380). No other associations were found between marihuana use and other cancers however the study was limited by the demographics of the HMO clientele and the low marihuana exposures. A case-control study suggested that marihuana use may increase the risk of head and neck cancer (OR 2.6; CI 1.1-6.6) with a strong dose-response pattern compared to non-smoking controls (381). The authors note a number of limitations with their study such as underreporting, inaccurate marihuana dose reporting, assay sensitivity and low power. A large 2006 population-based case-control study of 1,212 incident cancer cases and 1,040 cancer-free matched controls did not find a significant relationship between long-term cannabis use and cancers of the lung and upper aerodigestive tract (382). However, a smaller 2008 case-control study in young adults ($\leq$ 55 years of age) examining 79 cases of lung cancer and 324 controls reported that the risk of lung cancer increased 8% (95% CI 2-15%) for each joint-year of cannabis smoking after adjusting for cigarette smoking (383).

8.2 Respiratory tract

Mucosal biopsy specimens taken from chronic marihuana smokers who reported only smoking marihuana showed a number of histopathologic changes including basal cell hyperplasia, stratification, goblet cell hyperplasia, cell disorganization, inflammation, basement membrane thickening, and squamous cell metaplasia (384). However, the study employed a small number of subjects and relied on the accuracy and integrity of the subjects' recall to establish smoking status, as well as frequency and duration of smoking. Epidemiological studies have found mild changes in pulmonary function in heavy cannabis smokers, including reduction of forced expiratory volume in 1 second (FEV_1), increase in airway resistance and decrease in airway conductance (385,13,386). Heavy chronic cannabis smokers presented with symptoms of bronchitis, including wheezing, production of phlegm and chronic cough and long-term cannabis smoking may be a risk factor for chronic obstructive pulmonary disease in later life (30,387). All changes were most evident in heavy chronic users, defined as those who smoked more than 3 joints per day for 25 years (380,388). The effects on the respiratory tract defence system may increase the risk of infection in chronic users (389) however further epidemiological research is required to establish a causal relationship between marihuana smoking and respiratory infection.

8.3 Immune system

Cannabinoids appear to have powerful anti-inflammatory and immune-suppressive properties (390), however, the effects of marihuana smoking on the immune system in humans are less clear. A major concern with HIV-positive marihuana smokers is that they might be more vulnerable than other marihuana smokers to the immunosuppressive effects of marihuana or that they risk exposure to infectious organisms associated with marihuana plant material (116). A group of studies has partially addressed the former concern. In one study, HIV-positive patients on stable antiretroviral therapy randomized to smoked marihuana or dronabinol showed no changes in CD4+ and CD8+ T-cell, B cell, or NK cell counts and a number of other parameters compared with placebo over a 21-day study period (391). A longitudinal study of 481 HIV-infected men who used marihuana and who were followed over an average 5-year period found that while marihuana use was generally associated with a higher CD4+ cell count in infected men and

controls, no clinically meaningful associations, adverse or otherwise, between marihuana use and T-cell counts and percentages could be established (392). Marihuana use was also not associated with an increased rate of progression to AIDS in HIV-infected individuals (393). In another study, smoking marihuana was associated with lower plasma concentrations of the protease inhibitors (PI) indinavir and nelfinavir; dronabinol or placebo had no effect (85). However, the decreased PI levels were not associated with an elevated viral load or changes in CD4+ or CD8+ cell counts (132). Nevertheless, results from *in vitro* and *in vivo* experiments in animals suggest cannabinoids have an impact on virus-host cell interactions (394); cannabinoid treatment was associated with increased viral replication of HSV-2, HIV-1, KSHV, influenza, and VSV viruses or with increases in surrogate measures of infection in these models (395,396,397,398,399,400). In humans, smoking marihuana was associated with poorer outcome in patients with chronic hepatitis C (401,402). Caution should also be exercised when prescribing marihuana to patients undergoing cancer chemotherapy and whose immune systems may be compromised (116).

8.4 Reproductive and endocrine systems

Results from human epidemiological studies examining short-term neonatal outcomes among women who smoked cannabis during pregnancy are equivocal; some report reduced neonatal birth weight and length (403,404,405,406) or a slightly increased risk of sudden infant death (407), while others report no effect (408,409,410). On the other hand, there appear to be some long-term effects on the development of children born to mothers who used marihuana during pregnancy. Two longitudinal investigations over 20 years (reviewed in (368)), and confirmed by a third (369), suggest that such *in utero* exposure impacts negatively on attentional behaviour and visual analysis and hypothesis testing but not on standardized derived IQ scores. These behavioural effects also appeared to have a negative influence on aspects of executive function in later years.

Evidence suggests that cannabinoids accumulate in the breastmilk of mothers who smoke cannabis and are transferred to newborns through breastfeeding (370,411). In a case-control study (412), exposure to marihuana from the mother's milk, during the first month postpartum, appeared to be associated with a decrease in infant motor development at one year of age.

The effects of marihuana and THC on human sperm have been investigated both *in vivo* and *in vitro* (413,414,415). A significant decline in sperm count, concentration and motility and an increase in abnormal sperm morphology were observed in men who smoked marihuana (8-20 cigarettes/day) for 4 weeks (413). In an *in vitro* study, sperm motility and acrosome reactions were decreased in both the 90% and 45% sperm fractions; the 90% fraction being the one with the best fertilizing potential and the 45% fraction being a poorer subpopulation (415). Decreased sperm motility was observed in both fractions at THC concentrations mimicking those attained recreationally (0.32 and 4.8 μM) and in the 45% fraction at THC concentrations typically seen therapeutically (0.032 μM). Inhibition of the acrosome reaction was only observed at the highest THC concentration tested (4.8 μM) in the 90% fraction while the 45% fraction displayed decreased acrosome reactions at all three THC concentrations. Such effects carry the possibility of impairing crucial sperm functions and male fertility, especially in those males already on the borderline of infertility (415).

8.5 Cardiovascular system

The most consistent acute physiological effect of smoking marihuana is dose-related tachycardia (416). While this is not usually considered dangerous for healthy young users, it may be problematic to those already suffering from cardiac disorders or angina (27). Inhalation of cannabis smoke reduces the amount of exercise required to cause an angina attack by 50% (417) and has been associated with an increased relative risk of nonfatal myocardial infarction in the first hour following smoking (418). This may be caused by a THC-related increase in cardiac output, myocardial oxygen demand, catecholamine levels, carboxyhemoglobin as well as postural hypotension (416,419,420). While tachycardia is observed in both occasional and chronic users, tolerance develops relatively quickly with the degree of tachycardia diminishing with use. After about 8 to 10 days of constant dosing with 10 mg of THC per day (equivalent to 80-100 mg of marihuana containing 10% THC), bradycardia with a decrease in supine blood pressure was observed (421).

Cannabis is also known to cause peripheral vasodilation, postural hypotension, and characteristic conjunctival reddening after smoking (422).

AIDS patients may be at an increased risk of experiencing adverse cardiovascular outcomes caused by interactions between cannabis and antiretroviral drugs, such as ritonavir, which has been associated with adverse cardiovascular events (423).

8.6 Liver

Recent studies have strongly implicated the endocannabinoid system in chronic liver disease (424,425,426,427,428). Studies in patients with chronic hepatitis C, found a significant association between daily cannabis smoking and moderate to severe fibrosis (402), as well as being a predictor of fibrosis progression (401). Another study showed that daily cannabis use was a predictor of steatosis severity in these individuals (372). Steatosis is an independent predictor of fibrosis progression and an established factor of poor response to antiviral therapy (429). The authors recommend that patients with ongoing chronic hepatitis C be strongly advised to abstain from daily cannabis use. In contrast, a study by Sylvestre et al. (430), showed that modest cannabis use (defined as anything less than daily use) may offer symptomatic and virological benefit to some patients undergoing hepatitis C treatment.

8.7 Central nervous system

The most frequently reported adverse events for cannabinoids involve the central nervous system (CNS). Commonly encountered CNS events in controlled clinical trials with Marinol® and Sativex® are intoxication-like reactions including drowsiness, dizziness and transient impairment of sensory and perceptual functions (53,55). A "high" (easy laughing, elation, heightened awareness) from Marinol® was reported in 24% of the patients receiving it as an antiemetic and in 8% of patients receiving it as an appetite stimulant (53). Dizziness is the most common intoxication effect with Sativex® reported initially in 35% of patients titrating their dose; the reported incidence of this effect in long-term use is approximately 25% (431). All other intoxication-like effects are reported by less than 5% of users (with the exception of somnolence 7%) (431). Other events reported for Sativex® include disorientation and dissociation. CNS events for Marinol® also include paresthesias, visual distortions (all at 3%), paranoia, depersonalization (each 2%) and disorientation with confusion (1%) (55).

8.7.1 Cognition

The effects of cannabis use on cognition have been reviewed by Lundqvist (432). Marihuana impairs cognition involving short-term memory, attention, concentration, executive functioning and visuoperception (433,365,434). The digit span task has been used to estimate the effects of cannabis on recent memory, but results have been inconsistent. Differences may be due to the dosage used, the smoking procedure or whether the digit span task assesses forward or backward recall (435). Cannabis intoxication significantly impairs the ability to learn and recall word lists or short stories (436).

The long-term effects of cannabis on cognition remain controversial. Some studies report a positive association between cannabis consumption and cognitive deficits (437,438,439) or suggest that cognitive deficits persist after abstinence (440,441,433,365), whereas others did not find an association between cannabis use and long-term cognitive decline (440,441). Methodological limitations and the absence of powerful effects have contributed to difficulties in assessing the effects of chronic use and may help explain the discrepancies among studies (442,443). Nonetheless, studies generally suggest that chronic users of marihuana suffer varying degrees of cognitive impairment that have the potential to be long-lasting (35).

8.7.2 Psychomotor performance

Cannabis exposure impairs psychomotor performance (27) and patients must be warned not to drive after smoking marihuana. A double-blind, placebo-controlled, crossover study comparing the effects of a medium dose of dronabinol (20 mg) and of two hemp milk decoctions containing medium (16.5 mg) or high doses (45.7 mg) of THC reported severe impairment on several performance skills required for safe driving (444). Performance impairment appears to be less significant among heavy cannabis users compared to occasional users (27). It has been suggested that, unlike alcohol, cannabis users are aware of their level of intoxication and compensate by becoming hyper-cautious; in tasks such as driving this kind of behaviour results in decreased speed, decreased frequency of overtaking, and an increase in following distance (445,446). Others disagree with this assertion (447). In any case, individuals are affected differently by prolonged exposure to marihuana and there is some evidence of greater psychomotor effects on adolescents (448).

8.7.3 Psychiatric effects

8.7.3.1 Acute reactions

Cannabis use has been linked to episodes of acute psychosis in both regular and drug-naïve users. Two case reports of healthy subjects who had participated in a randomized controlled trial (RCT) measuring the effects of orally administered cannabis (including dronabinol or cannabis decoctions) on psychomotor performance displayed acute psychotic reactions following exposure to cannabis (449). The subjects had no psychiatric history or concomitant drug use but were "occasional" regular cannabis users. In another RCT, 22 healthy subjects also with a history of occasional cannabis use, no concomitant drug use, and with no psychiatric disorders received intravenous doses of Δ^9-THC paralleling peak plasma THC levels achieved by smoking cannabis cigarettes containing 1-3.5% Δ^9-THC (450). Drug administration was associated with a range of acute, transient, behavioural and cognitive effects including suspiciousness, paranoid and grandiose delusions, conceptual disorganization, and illusions. Depersonalization, derealization, distorted sensory perceptions, altered bodily perceptions, feelings of unreality and extreme slowing of time were also reported. Furthermore, blunted affect, reduced rapport, lack of spontaneity, psychomotor retardation, and emotional withdrawal were observed. Another study reported similar results (451). Similar short-term psychotic reactions have also been documented in some naïve cannabis users (452,30,449).

8.7.3.2 Depression

While the link between the use of marihuana and depression is a growing area of concern, research on this topic is relatively scarce and conflicting. A 2003 review reported that the comorbidity level between heavy or problematic cannabis use and depression in surveys of the general population exceeds what would be expected by chance (453). The authors also identify a modest association between early-onset regular or problematic use and later depression. However, limitations in the available research on cannabis and depression, including study design, as well as the measurement of cannabis use and depression were also highlighted. A U.S. study of adults (454) using longitudinal national survey data (n= 8 759) found that the odds of developing depression in past-year marihuana users was 1.4 times higher than the odds of non-users developing depression. However, after adjusting for group differences, the association was no longer significant. In a 2008 study, the same group looked at the relationship between cannabis use and depression among youth using a longitudinal cohort of 1 494 adolescents. Similar to the adult study, the results did not support the causal relationship between adolescent-onset cannabis use problems and early adult depression (455). In contrast, another U.S. study (456) based on the results of the National Epidemiological Survey on Alcohol and Related Conditions (n= 43 093), found major depression was significantly associated with lifetime cannabis disorders and dependence. A 2007 study using data from the Netherlands Mental Health Survey and Incidence Study did find a modest increased risk of a first depressive episode (OR 1.62; 1.06-2.48) after controlling for strong confounding factors (457). Of greater significance in this study, was the strong increased risk of bipolar disorder (OR 4.98; 1.80-13.81) with cannabis use. There was a dose-response relationship associated with the risk of 'any mood disorder' for almost daily and weekly users but not for less frequent users. A survey of 248 French high school students found cannabis users had significantly higher rates of suicidal behaviours, depressive and anxious symptoms compared to cannabis non-users (458). In conclusion, while a relationship between cannabis and depression may exist, more studies are needed to establish a causal relationship.

8.7.3.3 Schizophrenia and psychosis

Individuals with schizophrenia or with a family history of this disorder are likely to be at greater risk of suffering adverse psychiatric effects from marihuana (364). Interestingly, genetic studies indicate a link between allelic variants of the cannabinoid receptor gene (CNR1) and susceptibility to mood disorders (459,460). Heavy marihuana use can aggravate psychotic symptoms and cause more relapses and those who use marihuana are at an increased risk of a poor prognosis (461,462,315,27). Self-reported use of cannabis in adolescence has been associated with an increased risk of developing schizophrenia and this risk was related to frequency of marihuana exposure (463). A cohort study of over 1000 children, followed from birth to age 26, reported a three-fold increased risk of psychotic disorders in those who used cannabis and suggested that cannabis exposure among psychologically vulnerable adolescents should be strongly discouraged

(464). The relationship between cannabis use and psychotic symptoms was also studied in a cohort of 2 437 young people (14-24 years) with greater than average predisposition for psychosis and who had first used cannabis during adolescence (465). The authors found a dose-response relationship between frequency of cannabis use and the risk of psychosis. The effect of cannabis use was also much stronger in those individuals with a predisposition for psychosis. Although cannabis use increases the risk of psychosis, it is only one factor in a larger constellation of contributing factors (466). A systematic review of evidence pertaining to cannabis use and the occurrence of psychotic or affective mental health outcomes reported an increased risk of any psychotic outcome in individuals who had ever used cannabis compared with non-users (OR = 1.41) (317). Furthermore, the findings appeared to show a dose-related effect, with greater risk to individuals who used cannabis most frequently (OR = 2.09).

8.7.3.4 Amotivational syndrome

This syndrome is used to describe people who show little interest in school, work or other goal-oriented activity as well as withdrawing from social activities (27). To date, there is no convincing evidence to show a causal relationship between marihuana use and such behavioural characteristics (27). Rather, it appears that this constellation of behaviours is the result of chronic cannabis intoxication; de-intoxication results in resolution of symptoms (364,467).

8.8 Tolerance and dependence

Tolerance to most of the effects of marihuana can develop after a few doses and it also disappears rapidly following cessation of administration (27). In normal subjects, tolerance develops to the effects of marihuana on mood, intraocular pressure, EEG, psychomotor performance, nausea as well as on the cardiovascular system (468,469). The dynamics of tolerance vary with respect to the different effects; tolerance to some of the effects develops more readily and rapidly than others (470). In one study, tolerance to some of the cannabis effects developed both when THC was administered orally (30 mg four times a day) and when a roughly equivalent dose was given by smoking (3.1% cigarette; 5 puffs of 10 seconds each) (471). While both groups became tolerant to the "high", there was no diminution of the appetite stimulating effect from either route of administration.

There is evidence that cannabis dependence occurs with chronic heavy use (30,373). In the DSM-IV-TR, the term 'dependence', is closely related to the concept of addiction which may or may not include physical dependence and is characterized by use despite harm and loss of control over use (472). Physical dependence may also occur resulting in withdrawal symptoms when use is discontinued. Withdrawal symptoms appear within the first one to two days following discontinuation of cannabis use (smoked or oral), peak effects typically occur between days 2 and 6 and most symptoms resolve within 1-2 weeks (473). The most common symptoms include anger or aggression, irritability, anxiety, restlessness, decreased appetite or weight loss, and sleep difficulties. Less common symptoms include depressed mood, chills, stomach pain, shakiness and sweating.

9.0 Overdose/Toxicity

LD_{50} values for rats administered single oral doses of THC or crude marihuana extract are approximately 1000 mg/kg (474). Dogs and monkeys are able to tolerate significantly higher oral doses of THC or marihuana extract of 3000 mg/kg (or greater in certain cases) (474). The estimated human lethal dose of intravenous THC is 30 mg/kg (2100 mg/70 kg) (53). Significant CNS symptoms are observed with oral doses of 0.4 mg/kg Marinol® (53). Cannabis often produces unwanted physical effects, typically dizziness, sedation, intoxication, clumsiness, dry mouth, lowered blood pressure or increased heart rate (475). These adverse effects are generally tolerable and not unlike those seen with other medications (27). The rare acute complications (such as panic attacks, psychosis, convulsions, etc.) that present to the Emergency Department can be managed with conservative measures (476). As is stated in the case of overdose with Marinol® (53), the signs and symptoms observed with smoked marihuana are an extension of the psychotomimetic and physiologic effects of THC. If disturbing psychiatric symptoms occur at the prescribed dosage, the patient should be closely observed in a quiet environment and supportive measures, including reassurance, should be used.

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