RESEARCH PLAN FOR MARIJUANA FOR MEDICINAL PURPOSES: A STATUS REPORT

Therapeutic Products Programme
Health Canada

June 9, 1999

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PURPOSE

The purpose of this document is to lay out a research plan for determining the risks and benefits of the use of marijuana for medicinal purposes. This plan includes the following elements:

- a research agenda composed of several projects to address the issues of the safety and efficacy of smoked marijuana[1] and of cannabinoids[2];
- several mechanisms for access outside of the research projects; and
- activities to develop a Canadian source of research-grade marijuana.

INTRODUCTION

Some Canadians are requesting legal access to smoked marijuana for medicinal purposes. While there are anecdotal reports of the therapeutic value of smoked marijuana, scientific studies supporting the safety and efficacy of marijuana for therapeutic purposes, to date, are inconclusive. There is a need for further scientific studies. The current Canadian drug regulatory framework provides processes by which any substance, including marijuana, could be legally distributed provided the product is of good quality, originates from a licit licensed supplier, and is used in a proper research context.

Presently, marijuana is not approved as a therapeutic drug in any country of the world. Canadian research activities will contribute to on-going international scientific research into the medical uses of marijuana. All of the resulting new evidence will inform the debate over the use of legitimate, alternative therapeutic options and appropriate regulatory mechanisms.

[1] Marijuana or cannabis refers to unpurified plant substances including leaves or flower tops.

[2] Cannabinoids means the group of compounds related to THC (delta-9-tetrahydrocannabinol), whether found in the marijuana plant, in animals, or synthesized in laboratories.

BACKGROUND - CANNABIS AS A POTENTIAL MEDICINE

Marijuana - the plant

Marijuana, hashish, and hash oil are generally derived from the plant *Cannabis sativa*. Like most plants, cannabis is a variable and complex mixture of biologically active compounds. The plant contains more than 400 chemicals of which approximately 60 are called cannabinoids. The main psychoactive substance is generally believed to be THC (delta-9-tetrahydrocannabinol). Varying proportions of other cannabinoids, mainly cannabidiol (CBD) and cannabinol (CBN), are also present in cannabis, sometimes in quantities that might modify the effects of THC or cause effects of their own (NIH Symposium, 1997). In addition to the many chemical compounds which make up the cannabis plant, illicit cannabis may contain both adulterants added by those cultivating and processing the plant and naturally occurring contaminants such as microbes and fungi (British Medical Association, 1997).

Therapeutic uses often claimed for marijuana

Marijuana has been claimed to relieve symptoms associated with the following medical conditions:

- **Nausea and vomiting**: for the relief of nausea and vomiting associated with cancer and AIDS therapies;
- **Wasting syndrome**: to stimulate appetite and produce weight gain in AIDS and cancer patients;
- **Multiple sclerosis:** for the relief of muscle pain and spasms;
- **Epilepsy:** to help reduce the frequency of epileptic seizures; and
- **Glaucoma:** to lower intra ocular pressure.

Marijuana is also believed to alleviate numerous symptoms, ailments or disorders. These may include: chronic pain, spasticity produced by partial spinal cord injury, and intractable hiccoughs (an uncommon complication of AIDS).

Available clinical data on marijuana

Marijuana is not approved as a therapeutic product in any country of the world. To date, there have been few clinical trials worldwide on the use of marijuana for medicinal purposes. In recent years, the existing knowledge with respect to this issue has been assessed by several health and governmental organizations in various countries as well as by the World Health Organization (WHO). According to reports from these organizations, evidence of the potential therapeutic

efficacy of smoked marijuana is heavily anecdotal.[3, 4]

Available clinical data on cannabinoids

There are two commercially available drug products related to marijuana: dronabinol, (brand name, MARINOL®), which contains chemically synthesized THC; and a synthetic cannabinoid, nabilone (brand name, CESAMET®). In Canada, both drug products are approved for the treatment and management of severe nausea and vomiting associated with cancer chemotherapy and may be prescribed by physicians. These products are administered orally. Available data indicates a potential therapeutic value for cannabinoid drugs, particularly for symptoms such as pain, nausea and vomiting in situations other than those associated with cancer chemotherapy, and weight loss related to HIV disease or therapy.

CANADIAN REGULATORY FRAMEWORK

The current regulatory framework creates a scheme by which marijuana could be distributed and used for research purposes provided the product is of good quality, originates from a licit supplier and is used in a proper scientific context.

Regulation of marijuana

Marijuana for medicinal purposes is regulated under the *Controlled Drugs and Substances Act* (*CDSA*)[5], the *Narcotic Control Regulations* (*NCR*), the *Food and Drugs Act* (*F&DA*) and the *Food and Drug Regulations* (*F&DR*). The *CDSA* and its regulations provide a framework for the control of substances that can alter mental processes and that may produce harm to the health of individuals and to society as a whole when distributed or used without supervision. The *F&DA* and its regulations provide a framework to ensure that therapeutic products marketed to Canadians are safe, effective and of high quality.

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[3] A recent report by the US Institute of Medicine (IOM) entitled, *Marijuana and Medicine: Assessing the Science Base* is available: http://www2.nas.edu/whatsnew/29de.html

[4] *Cannabis: the scientific and medical evidence.* The Report of the UK House of Lords, Select Committee on Science and Technology, Session 1997-98, 9th Report, HL Paper 151, November 1998, is available on the web at http://www.parliament.the-stationery-office.co.uk/pa/ld199798/ldselect/ldsctech/151/15101.htm

[5] The *CDSA* came into force on May 14, 1997.

The *Controlled Drugs and Substances Act* (*CDSA*) and its Regulations

Cannabis, its preparations, derivatives and similar synthetic preparations are listed under Schedule II to the *CDSA*. Except as authorized under the *Narcotic Control Regulations (NCR)*, the possession, possession for trafficking, trafficking, importation, exportation, possession for exporting and production of narcotics, including marijuana, is prohibited under the *CDSA*. The *NCR* authorize various persons or institutions (e.g., licensed dealers, pharmacists, physicians and hospitals) to carry out certain activities which are otherwise illegal under the *CDSA* by creating a legal chain of distribution for controlled substances, including marijuana, to permit, among other things, their use for research purposes.

It is important to note that even if a new therapeutic drug can legally be sold or distributed under the *F&DA* and Regulations, it does not mean that its sale, distribution or possession is legal under the *CDSA*. Conversely, even if a manufacturer is licensed under the *CDSA* and the *NCR*, it does not mean that the drug is approved for sale and distribution as a therapeutic product in Canada. The requirements under both statutes and underlying regulations need to be met to legally authorize marijuana to be used for medicinal purposes.

The sale and distribution of marijuana is subject to the same regulations as those that apply to morphine. However, contrary to marijuana, the safety and efficacy of morphine has been established for specific medical conditions. In addition, medicinal-quality morphine is produced and distributed by licit licensed manufacturers in accordance with Good Manufacturing Practices (GMP).

The *Food and Drugs Act* (*F&DA*) *and Regulations*

Since the safety and efficacy of marijuana as a medicine has not been demonstrated in any country of the world, the first step under the *F&DA* is to gather scientific information and in particular, to conduct clinical trials. Prior to initiating a clinical trial, sponsors are required to submit a research proposal in the form of an Investigational New Drug Submission (IND).

An INDS includes, but is not limited to, the following information: the names of the clinical investigators, the rationale for the study, a complete study protocol (defining the study objectives, design, number of patients to be studied, treatment plan, dosage regimen, patient inclusion and exclusion criteria, safety monitoring, efficacy parameters, statistical plan, etc.), as well as information on the chemistry and manufacturing of the drug (including the specific dosage form(s) and strength(s)). This information is reviewed by the Therapeutic Products Programme (TPP) within Health Canada to ensure that the design of the study is appropriate to test the hypothesis and that participants are not exposed to undue risk. The assessment also ensures that the clinical trial adheres to Canadian and international ethical and scientific standards and that the product is manufactured to ensure purity and concentration.

A RESEARCH PLAN FOR THE MEDICAL USE OF MARIJUANA

Health Canada's research plan has been developed with advice from the Therapeutic Products Programme's (TPP) external Expert Advisory Committee on New Active Substances (EAC/NAS).[6] The Minister of Health has requested that a status report be prepared to provide details of the work-in-progress on this important set of initiatives.

I. Structured Research Projects

The proposed research plan consists of three projects.

(a) Research using smoked marijuana: the Community Research Initiative of Toronto (CRIT) [7] and the Canadian HIV Trials Network (CTN)[8]

The Canadian HIV Trials Network is a partnership committed to developing treatments, vaccines and a cure for HIV disease and AIDS, through the conduct of scientifically sound and ethical clinical trials. The Community Research Initiative of Toronto with the CTN partners will coordinate these activities. Ideally, a multi-center research design would permit eligible Canadians outside of Toronto to participate in the clinical trials. The details of the protocol, such as the inclusion criteria and number of subjects required, are being developed. Health Canada has committed funding for short-term clinical trials using smoked marijuana.

Currently, the US National Institute of Drug Abuse (NIDA)[9] is the only supplier of research-grade marijuana cigarettes available for researchers. NIDA has established a drug supply system by which US and foreign researchers may gain access to certain drugs including marijuana cigarettes and cannabinoids. Officials within the Therapeutic Products Programme will be assisting researchers to obtain access to a source of research-grade marijuana for use in clinical research conducted in Canada. Researchers will not be required to contact NIDA directly; Health Canada will be the only authorized contact and

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[6] Terms of Reference, membership and minutes from the EAC/NAS meetings are on the TPP website at http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/advcomm_eacnas.html

[7] Information on CRIT is available at http://www.web.net/~crit/index.html

[8] Information on the Canadian HIV Trials Network is on the web at http://www.hivnet.ubc.ca/ctn.html The CTN toll-free information telephone number is 1-800-661-4664.

[9] NIDA is one of the U.S. National Institutes of Health. They are accessible on the web at http://www.nida.nih.gov/ On May 21, 1999, NIDA issued a guidance document on the provision of marijuana for medical research. It is on the web at http://www.nih.gov/grants/guide/notice-files/not99-091.html

will manage the distribution system. Shortly after the study protocol has been finalized and authorized, and research-grade marijuana has been obtained, research can begin.

(b) Research using other marijuana extracts and components: Medical Research Council of Canada

The Medical Research Council of Canada (MRC) is the major federal agency responsible for funding biomedical research in Canada. The MRC does not operate laboratories of its own. Rather, the research it supports is carried out by scientists in universities, hospitals and research institutes across the country.

Health Canada has committed funds so that the MRC can sponsor clinical trials as well as other basic and applied research activities, pertaining to marijuana, extracts and related products, subject to approval by the Council. The MRC will post a notice of Requests for Proposals on its web site by the end of June, 1999, with a submission deadline of September 15, 1999. Successful proposals could be funded early in the new year. Researchers who are interested in submitting a proposal should review existing scientific literature and monitor the MRC's web site for specific instructions.

(c) Research using non-smoked marijuana: GW Pharmaceuticals (U.K.)

The Therapeutic Products Programme is considering a proposal from GW Pharmaceuticals to conduct clinical trials on inhaled cannabinoids with the following objectives:

- to make available legal, cannabis-based medicines to Canadian patients by establishing a clinical research programme and long term safety monitoring;
- to allow a research programme to proceed in the Canadian public's interest by replicating the legal, regulatory and ethical framework that has been established in the UK. This will be in accordance with Canadian law, the Single Convention on Narcotic Drugs (1961) and the domestic regulatory and ethical framework;
- to evaluate delivery methods other than smoking and to generate data on quality, safety and efficacy of a scope and standard satisfactory for peer review publication; and
- to establish a pilot programme (100 patients) which can be expanded if required to a full programme eventually leading to a licensed prescription medicine.

GW Pharmaceuticals is a British company which currently holds a license from the

UK Home Office to cultivate research-grade marijuana plants for use in research studies in the UK, under specific conditions established by the Home Office. GW Pharmaceuticals has already initiated the cultivation of research-grade marijuana. The company is developing various marijuana extracts to be delivered through an inhalation device. The company believes that its product would offer the advantage of an inhaled (non-smoked) form of drug without the harmful by-products of the smoked form. Pending the outcome of the review of GW Pharmaceutical's proposal, there will be an announcement providing details about the research protocol with contact information.

II. Other Mechanisms for Access Outside of Research Projects

Given the need to address humanitarian considerations and the public's demand for compassionate access to smoked marijuana, it is important to highlight mechanisms by which Canadians may have access to drugs other than through clinical trials. These mechanisms include the Special Access Programme (SAP) and the Exemption for Medical Purposes under section 56 of the *CDSA*.

Special Access Programme (SAP)[10]

The *F&DR* enable the Canadian regulator to make substances that have not yet been approved for marketing in Canada accessible, for compassionate use, to physicians. The Special Access Programme, as managed by the TPP, allows physicians to gain access to drug products on a patient-by-patient basis, if the physician believes that conventional therapies have failed, are unavailable in Canada or are unsuitable.

The SAP routinely authorizes access to controlled and narcotic substances. In each of these cases the authorization is for a drug product, in dosage form, and manufactured by a credible, licensed establishment which adheres to national and international drug manufacturing standards. These standards guarantee that drug substances are available in known and consistent concentrations. The TPP's role, as a federal institution, is to ensure that physicians' requests and patients' needs are legitimate in each case and that the substance is generally safe and of good quality. A physician's decision that alternative therapies are not appropriate is considered to be the practice of medicine and falls under provincial jurisdiction.

Currently, there is no licit, licensed, non-governmental supplier anywhere from whom research-grade marijuana can be obtained under the SAP. In some countries, including the USA and the UK, marijuana is being legally cultivated in limited quantity and under strict government controls but its availability is restricted to research purposes. In addition, any importation or production will be undertaken in compliance with Canada's international commitments under the United Nations Single Convention on Narcotic Drugs, 1961.

[10] Information on the SAP is on the web at: http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/edrp.html

Exemption Under s.56 (*CDSA*) for Medical Purposes

Section 56 of the *CDSA* gives the Minister of Health the discretionary power to grant, in specific cases, an exemption from the application of any or all parts of the *CDSA* or its regulations if, in the opinion of the Minister, the exemption is necessary for medical or scientific purposes or is otherwise in the public interest.

An Interim Guidance Document was published in early May, 1999, to assist individuals who want to apply for an exemption for medical purposes.[11] This document details the information that should be included in an application for exemption to allow for a fair and complete review of each request. As of June 3, 1999, just over thirty requests have been made under section 56 of the *CDSA* for medical purposes. After all of the required information has been submitted, the Department aims to review the request within 15 working days. The Minister's decision to exercise discretion for each case is made in the context of the recommendation formulated as part of the review and the circumstances of each individual applicant.

Special Considerations

Under both the *CDSA* and the *F&DA*, there are already processes and controls in place that apply to marijuana distribution and possession for medicinal purposes. The *NCR* allow certain persons to distribute narcotics that they licitly have in their possession. For instance, subject to certain conditions, licensed dealers may supply narcotics to pharmacists or practitioners who may in turn supply the drugs pursuant to a prescription to patients. The *NCR* do not permit any further distribution of the drugs by patients. The *NCR* processes for distribution aim at providing an adequate control over the drugs to prevent misuse and illicit trafficking. These schemes would also apply to marijuana from a licit licensed dealer.

The *F&DR* also provide various avenues by which drugs intended for therapeutic purposes may be distributed (i.e., general marketing, clinical trial and SAP). The *Regulations* make provisions for specific distribution paths which aim to ensure that drugs distributed to Canadians are safe, effective and of high quality.

Although the existing processes and controls applicable to the possession and distribution of controlled substances are generally adequate, marijuana, because of its unique nature (i.e., a smoked product, psychoactive, with a high street value) requires additional terms and conditions to specific activities proposed. Health Canada will determine, on a case-by-case basis, the necessity of imposing other terms and conditions, particularly for use within the research context. For instance, the following may apply:

- participants in research studies and possessing marijuana (smoked form) will be strongly

[11] The Interim Guidance Document is posted on the Health Canada web site at http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/cds/guides/interim_e.html

encouraged to consent to the release of their name, date of birth and address to Health Canada and law enforcement agencies. This will assist in avoiding police intervention where the substance is lawfully possessed. This personal information will be held in confidence.

- participants in research studies would be informed by the clinical investigators to take appropriate measures to ensure that others would not be exposed to the second-hand smoke.

- the quantity of marijuana that participants would be allowed to possess within the research studies would be limited.

- participants in research studies should be instructed by the clinical investigators to keep marijuana in a secure area and be reminded that they cannot distribute the marijuana to others.

III. Canadian Source of Research-Grade Marijuana

Sources of Marijuana

To protect the health and safety of Canadians and facilitate the generation of scientific data, research-grade marijuana must be of a reliable and consistent chemical composition and potency and originate from a licit supplier. Illicit marijuana, like other "street drugs" is often mixed or adulterated with unknown, harmful substances.[12] Some have suggested using embargoed, seized marijuana for medical research. The Commission of Narcotic Drugs General Assembly has resolved under the United Nations 1961 Convention that countries, including Canada, should refrain from the proliferation of supply sources and avoid unforeseen imbalances caused by sales of seized and confiscated drugs and products manufactured from such drugs. The long standing policy of the organization overlooking treaties compliance is that countries should not base a licit activity (i.e., research) upon an illicit source. Consequently, the idea of recycling marijuana seized in enforcement activities is not a viable option. Securing a licit source will ensure that the marijuana used in medical research is of an acceptable, standardized quality, free from fungi, molds, pesticides or other contaminants.

Securing a Governmental Source of Marijuana

Since a dependable source of research-grade marijuana is necessary to enable the conduct of clinical trials and given that NIDA may not entirely fill Canada's needs, Health Canada is taking steps to establish a government-controlled growing operation in Canada. The proposed supply of marijuana would be used solely for medical research purposes. A business plan is scheduled to be

[12] *Tamper Free Production of Marijuana for Medicinal Uses*, by M.M. Abdel-Monem, February 5, 1997. Washington State University, College of Pharmacy.

presented to and considered by Health Canada in the coming months.

Pharmaceutical Source of Cannabinoids

As mentioned in the background section there are two commercially available drugs related to marijuana: MARINOL® (dronabinol), which contains chemically synthesized THC; and CESAMET® (nabilone), a synthetic cannabinoid. Both drug products have been approved in Canada for the treatment and management of severe nausea and vomiting associated with cancer chemotherapy and may be prescribed by physicians.

Other natural and synthetic cannabinoids (e.g., cannabinol, levonantradol) are available to researchers for basic research and the development of new pharmaceutical route. These initiatives may, in the future, result in the development of new therapeutic products.

CONCLUSION

Health Canada's plan for marijuana for medicinal purposes consists of elements to address both scientific and medical research questions around the therapeutic value of marijuana. These research initiatives will help those who are suffering from terminal illnesses, for instance, and who believe that using marijuana, under controlled circumstances, could alleviate their symptoms and improve their quality of life. The Minister's authority to grant s. 56 exemptions for medical purposes under the *CDSA* is also a vehicle to ensure that requests from people in dire health crises are evaluated appropriately.

Notwithstanding the legal constraints involved, the proposed research initiatives, together with existing administrative procedures already in place in the Therapeutic Products Programme, provide the Minister of Health with a credible, balanced course of action. This course of action will be re-evaluated as new information becomes available. Elements of the initiative may be subject to change or revision as necessary.