OFFICES OF THE GOVERNORS

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WASHINGTON

November 30, 2011

Michele Leonhart, Administrator
Drug Enforcement Administration
Attn: Administrator
8701 Morrissette Drive
Springfield, VA 22152

Subject: ***Rulemaking petition to reclassify cannabis for medical use from a Schedule I controlled substance to a Schedule II***

Dear Administrator Leonhart:

Pursuant to Section 1308.43 of Title 21 of the Code of Federal Regulations (CFR), we hereby petition to initiate proceedings for the issuance of an amendment of a rule or regulation pursuant to Section 201 of the Controlled Substances Act (CSA). Specifically, we petition for the reclassification of medical cannabis (also known as marijuana) from Schedule I to Schedule II of the CSA.

Attached hereto and constituting a part of this petition are the following as required by the CSA and the CFR:

Exhibit A – The proposed rule. We seek the amendment of an existing rule, so pursuant to 21 C.F.R. §1308.43(6), we have included the existing rule together with a reference to the section in the CFR where it appears, along with our proposed amendment for your consideration.

Exhibit B – A statement of the grounds upon which we rely for the issuance of an amendment of the rule. As required, the grounds we rely on include a reasonably concise statement of the facts, including a summary of relevant medical or scientific evidence in the form of an eight factor analysis that the CSA specifies a petitioner must address (21 U.S.C. §811(c)). The Secretary of the United States Department of Health and Human Services (HHS) through the Food and Drug Administration (FDA) will consider these factors in a report to you for purposes of informing your final decision. The factors include: (1) actual and potential for abuse; (2) pharmacology; (3) other current scientific knowledge; (4) history and current pattern of abuse; (5) scope, duration and significance of abuse; (6) public health risk; (7) psychic or physiological dependence liability; and (8) whether it is an immediate precursor of a controlled substance.

The attached statement of grounds about the scientific and medical record, considering these eight factors, supports recognition of the accepted medical use of cannabis in the United States. Accordingly, we request you to open rulemaking to reschedule cannabis for medical purposes under the CSA from a Schedule I to a Schedule II controlled substance.

Background:

We are concerned that patients with serious medical conditions who could benefit from medical use of cannabis do not have a safe and consistent source of the drug. As you know, sixteen states and the District of Columbia have decriminalized cannabis for limited medical purposes. Each of these jurisdictions is struggling with managing safe access to medical cannabis for patients with serious medical conditions. Our work with the federal agencies has not resolved the matter. Federal enforcement policies acknowledge the "compassionate use" for seriously ill patients, but the policies do not provide means for safe access of medical cannabis for patients in need.

The divergence in state and federal law creates a situation where there is no regulated and safe system to supply legitimate patients who may need medical cannabis. State and local governments cannot adopt a regulatory framework to ensure a safe supply is available for – and limited to – legitimate medical use without putting their employees at risk of violating federal law. As some states seek to increase regulation, United States Attorneys have warned that the federal government would prosecute "vigorously against individuals and organizations that participate in unlawful manufacturing and distribution activity involving marijuana, even if such activities are permitted under state law." Yet in the absence of state or local regulatory systems, there exists wide spread confusion and proliferation of unregulated activities.

More to the point, it is clear that the long-standing classification of medical use of cannabis in the United States as an illegal Schedule I substance is fundamentally wrong and should be changed. The federal government could quickly solve the issue if it reclassified cannabis for medical use from a Schedule I drug to a Schedule II drug. Most recently the DEA, as noted in your letter dated June 21, 2011 (published July 8, 2011 in the Federal Register), denied a 2002 petition to initiate proceedings to reschedule marijuana based on an outdated 2006 HHS/FDA scientific review. With respect to marijuana, the 2006 HHS/FDA review found: (1) the medical substance has a high potential for abuse; (2) has no currently accepted medical use in treatment in the United States; and (3) lacks accepted safety for use under medical supervision.

Upon review of the enclosed petition, we believe you will find that the mounting evidence refutes the 2006 review and shows that: (1) cannabis for medical purposes has a relatively low potential for abuse, especially in comparison with other Schedule II drugs; (2) the medical community has concluded that cannabis has accepted medical use in treatment in the United States; and (3) cannabis has accepted safety for use under medical supervision and pharmacy based access. It is now the DEA's responsibility to make appropriate decisions and update the scheduling of drugs based on the changing scientific evidence and the opinion of the medical community. We submit that evidence herein.

The American medical community supports rescheduling, and there are safe pharmacy-based methods to dispense medical cannabis:

The medical community supports rescheduling medical cannabis. In 2009, the American Medical Association (AMA) reversed its earlier position that supported Schedule I classification of cannabis. The AMA now supports investigation and clinical research of cannabis for medicinal use, and urged the federal government to reassess the Schedule I classification. The American College of Physicians recently expressed similar support. A great many other groups also support rescheduling.

The National Academy of Sciences, Institute of Medicine perhaps states it best: "Marijuana is not, to be sure, a completely benign substance. It is a powerful drug that affects the body and mind in a variety of ways. However, except for the damage caused by smoking [*which this petition clearly describes non-smoking methods for medical use*], its adverse effects resemble those of many approved medications." [Italics added]

Categorizing medical cannabis as a Schedule II drug would also allow pharmacy dispensing. It requires federal changes to allow pharmacy dispensing and regulated manufacturing and distribution, otherwise pharmacies and pharmacists put their DEA license numbers at risk. There are acceptable methods to safely prescribe and dispense medical cannabis. A pharmacy based method is an existing and effective model that could provide safe and reliable access for patients in need, just like it provides for other controlled substances. The well regulated pharmacy system is perfectly suited to providing controlled access to drugs for legitimate medical use.

Recent scientific development like affordable DNA analysis also supports the pharmacy model. With modern DNA analysis, it is easy to obtain an accurate characterization of the plant's beneficial compound. At the pharmacy level, with current technology readily available today, a compounding pharmacist could easily and inexpensively quantify the levels of cannabinoids, and then use the appropriate cannabis blend to create a customized medication for an individual patient. Compounding is now increasingly offered by community pharmacies. Moreover, studies have shown that pharmacists providing compounding reported increased quality of pharmaceuticals and improved collaboration between the patient, physician, and pharmacist. This paradigm would allow safe access to a medicine with proven efficacy and acceptable safety, in a manner that does not endanger the patient and allows for reasonable governmental oversight. It is important to note that medical cannabis can be vaporized, not smoked. Additionally cannabis can be ingested orally, or applied topically in a liniment. These issues are fully addressed in Exhibit B.

Conclusion:

A public rulemaking process would allow all interested parties to contribute their comments and expertise, and provide a full record for decision. These interested parties include patients and medical professionals and the sixteen states and the District of Columbia, or nearly one-third of the nation's population, that have decriminalized limited possession and use of cannabis for serious medical conditions, and at least ten other states are considering similar measures.

While not required by the law, we urge you to hold public hearings on these issues even before making your decision on whether to initiate formal rulemaking proceedings. You will find that physicians and scientists, mayors and county executives, sheriffs and prosecutors, and the majority of Americans based on reliable national polling, believe rescheduling medical cannabis for serious illnesses is appropriate.

Medical cannabis does have a potential for abuse, but far less so than other Schedule II substances like opiates. There are well researched accepted medical uses; there are ways to safely administer the drug; and, there are effective non-smoking methods like vaporization, oral ingestion or topical application. The exhaustive medical and scientific report attached as Exhibit B, incorporating the necessary eight factors, shows rescheduling cannabis for medical purposes is appropriate.

Current federal rules preclude the adoption of reasonable and workable frameworks for providing access to patients while maintaining the ability of law enforcement agencies to address non-medical/illegal distribution and use of cannabis. The situation has become untenable for our states and others. The solution lies with the federal government. We urge the DEA to initiate rulemaking proceedings to reclassify medical cannabis as a Schedule II drug so qualifying patients who follow state law may obtain the medication they need through the traditional and safe method of physician prescribing and pharmacy dispensing.

Thank you for your consideration.

Sincerely,

Lincoln D. Chafee
Governor of Rhode Island

Christine O. Gregoire
Governor of Washington

Enclosures:

Exhibit A – Proposed Rule
Exhibit B – Statement of Grounds

cc: The Honorable Eric Holder, U.S. Attorney General
The Honorable Kathleen Sebelius, Secretary, U.S. Department of Health and Human Services
The Honorable Margaret Hamburg, M.D., FDA Commissioner

Please send all notices regarding this petition to:

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Submitted in quintuplicate pursuant to 21 C.F.R. §1308.43

Exhibit A: Proposed Rule

We propose the following: that the rule placing "marihuana" in Schedule I [21 CFR 1308.11(d)(23) and 21 CFR 1308.11(d)(31)] is repealed and placed as a Schedule II drug. This is not a petition for the removal of marijuana from scheduling under the Controlled Substances Act (CSA), but a petition to have marijuana and related items removed from Schedule I and rescheduled as "medical cannabis" in Schedule II, and made on the basis of the scientific and medical evaluation required pursuant to the CSA, *see* Exhibit B, Statement of Grounds (21 USC 811(c)).

For the purposes of this petition, and in reference to the Drug Enforcement Administration (DEA) listing of Schedule I drugs, this will include all tetrahydrocannabinols (THC), which are naturally contained in a plant of the genus Cannabis (cannabis plant), as well as synthetic equivalents of the substances contained in the cannabis plant, or in the resinous extractives of such plant, and/or synthetic substances (not otherwise already classified as Schedule II or III), derivatives, and their isomers with similar chemical structure and pharmacological activity to those substances contained in the plant, such as the following:

-1 cis or trans tetrahydrocannabinol, and their optical isomers;
-6 cis or trans tetrahydrocannabinol, and their optical isomers; and
-3,4 cis or trans tetrahydrocannabinol, and its optical isomers.

Given that nomenclature of these substances is not internationally standardized, compounds of these structures, regardless of numerical designation of atomic positions covered are included.

The following is the proposed rule:

REMOVE: 21 CFR 1308.11(d) (23) and (31) and others sections that may relate to medical cannabis use:

"(d) Hallucinogenic substances. …:

…~~(23) Marihuana~~	~~7360~~
…~~(31) Tetrahydrocannabinols~~	~~7370~~
~~Meaning tetrahydrocannabinols naturally contained in a plant of the genus Cannabis (cannabis plant), as well as synthetic equivalents of the substances contained in the cannabis plant, or in the resinous extractives of such plant, and/or synthetic substances, derivatives, and their isomers with similar chemical structure and pharmacological activity to those substances contained in the plant, such as the following:~~ - ~~-1 cis or trans tetrahydrocannabinol, and their optical isomers~~ ~~-6 cis or trans tetrahydrocannabinol, and their optical isomers~~	

~~3,4 cis or trans tetrahydrocannabinol, and its optical isomers~~

~~(Since nomenclature of these substances is not internationally standardized, compounds of these structures, regardless of numerical designation of atomic positions covered.)~~"

RESCHEDULED TO: 21 CFR 1308.12 Schedule II:

"(a) Schedule II shall consist of the drugs and other substances, by whatever official name, common or usual name, chemical name, or brand name designated, listed in this section. Each drug or substance has been assigned the Controlled Substances Code Number set forth opposite it.

…

(f) Hallucinogenic substances.

(1) …
(2) Cannabis (also known as Marihuana, including Tetrahydrocannabinols) for medicinal purposes only …

OTHER ISSUES FOR CONSIDERATION:

We would urge appropriate age and condition limitation.

Exhibit B: Statement of Grounds

Prepared by Gregory T. Carter, MD, MS,[i] Mitchell Earleywine, PhD,[ii] and Jason T. McGill, JD[iii]

Table of Contents:

Exhibit B: Statement of Grounds

STATEMENT OF GROUNDS (21 USC 811(c)):

To remove all forms of cannabinoid medicines that are currently in Schedule I classification by the Federal United States Drug Enforcement Agency (DEA) laws, as determined by the Controlled Substances Act (CSA), be rescheduled as "medical cannabis" in Schedule II, as necessitated and made on the basis of the scientific and medical evaluation required by the CSA and in accordance with existing law. For the purposes of this petition, and in reference to the DEA listing of Schedule I drugs, this will include all tetrahydrocannabinols (THC), which are naturally contained in a plant of the genus Cannabis (cannabis plant), as well as synthetic equivalents of the substances contained in the cannabis plant, or in the resinous extractives of such plant, and/or synthetic substances, derivatives, and their isomers with similar chemical structure and pharmacological activity to those substances contained in the plant, such as the following:

-1 cis or trans tetrahydrocannabinol, and their optical isomers;
-6 cis or trans tetrahydrocannabinol, and their optical isomers; and
-3,4 cis or trans tetrahydrocannabinol, and its optical isomers.

Given that nomenclature of these substances is not internationally standardized, compounds of these structures, regardless of numerical designation of atomic positions covered are included. For the remainder of this document, the terms cannabis and marijuana (also spelled "marihuana") will be used interchangeably to refer to any preparation of the cannabis plant intended for medicinal purposes. There are at least three species of the cannabis genus, those being cannabis sativa, cannabis indica, and cannabis ruderalis, any of which may be used for medicinal purposes.

Exhibit B: Statement of Grounds

BACKGROUND AND OVERVIEW OF EIGHT FACTOR ANALYSIS

Cannabis is now categorized (scheduled) by the DEA, as determined by the CSA, as a Schedule I drug. Schedule I is a category of drugs not considered legitimate for medical use because of limited utility and a high potential for dependence. Sharing this schedule with cannabis are heroin, lysergic acid, and methamphetamine. Schedule II is a category of drugs considered to have a strong potential for abuse or addiction but that also have legitimate medical use. Included here are opium, morphine, cocaine, and oxycodone. Schedule III drugs are felt to have even less abuse or addiction potential than Schedule I or II drugs and have a beneficial medical use. Included here are dronabinol, hydrocodone, amphetamine-based stimulants, and short-acting barbiturates. Schedule IV and V drugs are felt to have even less risks. Schedule IV drugs include benzodiazepines, while schedule V drugs include antidiarrheals and antitussives that contain opioid derivatives. While the DEA considers cannabis a schedule I drug, it classifies dronabinol (Marinol) as schedule III. Dronabinol is 100 percent THC and is potentially very psychoactive. Natural cannabis typically would be no more than 15 percent THC by weight. Thus it is inconsistent that cannabis, with 15 percent THC, remains a Schedule I drug, while dronabinol, at 100 percent THC, is schedule III.

Currently cannabinoid medicines fall into three categories: single molecule pharmaceuticals, cannabis-based liquid extracts, and phytocannabinoid-dense botanicals. It is this last category which is the primary target of this petition. The first category includes United States Food and Drug Administration (FDA)-approved synthetic or semisynthetic single molecule cannabinoid pharmaceuticals available by prescription. Currently, these are dronabinol, a Schedule III drug and nabilone, a Schedule II drug. Though both are also used off label, dronabinol, a (-)trans- 9-tetrahydrocannabinol (THC) isomer is found in natural cannabis and has been approved for two uses since 1985 and 1992 respectively: the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments and the treatment of anorexia associated with weight loss in patients with acquired immunodeficiency syndrome (AIDS).(179, 369) Nabilone, a synthetic molecule shaped similarly to THC, has also been approved since 1985 for use in the treatment of nausea and vomiting associated with cancer chemotherapy.(370, 473)

The second category of cannabinoid medicines being used in the United States includes a line of cannabis-based medicinal extracts developed by several companies. The industry leader is GW Pharmaceuticals, a United Kingdom-based biopharmaceutical company whose lead product is currently undergoing FDA-approved, multisite clinical trials for the treatment of opioid-refractory cancer pain after receiving prior approval for Phase III clinical trials in the United States.(601) This botanical drug extract which goes by the nonproprietary name nabiximols has already secured approval in Canada for use in the treatment of central

neuropathic pain in multiple sclerosis (in 2005) and in the treatment of intractable cancer pain (in 2007).(601)

This report presents scientific research organized by sections containing research reviews on the following eight factors required by the CSA that determine control of a drug or substance or its removal from schedules (21 USC 811(c)):

1. Actual and potential for abuse
2. Pharmacology[1]
3. Other current scientific knowledge
4. History and current pattern of abuse
5. Scope, duration and significance of abuse
6. Public health risk
7. Psychic or physiological dependence liability
8. If an immediate precursor of a controlled substance

CANNABIS SHOULD BE RESCHEDULED TO SCHEDULE II BECAUSE IT DOES NOT MEET THE REQUIREMENTS OF SCHEDULE I (21 U.S.C. 812(b)(1)):

Past DEA decisions not to reclassify cannabis have relied upon 21 U.S.C. 812(b)(1). Therefore, this report provides evidence to prove that cannabis fails to meet the three criteria for placing a substance in Schedule I of the CSA under 21 U.S.C. 812(b)(1) because:

1. Cannabis does not have a high potential for abuse compared with other Schedule II drugs;
2. Cannabis is currently accepted for medical use in treatment in the United States; and
3. Evidence is clear of accepted safety for use of cannabis under medical supervision.

ORGANIZATION OF REPORT:

Due to subject matter flow, the organization of the report discusses the necessary factors in this order: Factors two (Pharmacology), three (Other current scientific knowledge), and eight (If an immediate precursor), and then factors one (Actual and potential for abuse), four (History and current pattern of abuse), five (Scope, duration and significance of abuse), seven (Psychic or physiological dependence liability) and six (Public health risk).

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[1] This includes a sub-factor analysis regarding "currently accepted medical use." A drug has a "currently accepted medical use" if all of the following five elements have been satisfied:

A. The drug's chemistry is known and reproducible
B. There are adequate safety studies
C. There are adequate and well-controlled studies proving efficacy
D. The drug is accepted by qualified experts; and
E. The scientific evidence is widely available.

1. PHARMACOLOGY (FACTOR TWO)

The Secretary must consider the scientific evidence of the pharmacological effects of cannabis. There are abundant scientific data available on the neurochemistry, toxicology, and pharmacology of cannabis. This section and others includes a scientific evaluation of cannabis' neurochemistry, pharmacology, and human and animal behavioral, central nervous system, cognitive, cardiovascular, autonomic, endocrinological, and immunological system effects. The overview presented below relies upon the most current research literature on cannabinoids.

In describing the pharmacological effects of cannabis, this section also addresses the five elements of currently accepted medical use. Per the DEA, a drug has a "currently accepted medical use" if all of the following five elements have been satisfied(25):

A. The drug's chemistry is known and reproducible;
B. There are adequate safety studies;
C. There are adequate and well-controlled studies proving efficacy;
D. The drug is accepted by qualified experts; and
E. The scientific evidence is widely available.

These issues will now be addressed in full, as means to substantiate the argument that cannabis should be re-scheduled to schedule II.

Meeting the five-factor criteria for "currently accepted medical use":

A. The chemistry of cannabis is known and reproducible

The chemistry of cannabis is remarkably well-known and highly reproducible compared to other legal drugs. Cannabis is a complex plant, with several subtypes of cannabis, each containing over 400 chemicals.(10,16,18,102,615,616) Approximately 60 are chemically classified as cannabinoids.(19) Cannabinoids, consisting of alkylresorcinol and monoterpene groups, are unique secondary metabolites that are found only in Cannabis. The cannabinoids are 21 carbon terpenes, biosynthesized predominantly via a recently discovered deoxyxylulose phosphate pathway.(349) The cannabinoids are lipophilic and not soluble in water. Among the most psychoactive of the cannabinoids is delta-9-tetrahydrocannabinol (THC), the active ingredient in dronabinol.(19) Other major cannabinoids include cannabidiol (CBD) and cannabinol (CBN), both of which may modify the pharmacology of THC or have distinct effects of their own.(591) CBD is not psychoactive and has significant anticonvulsant, sedative, and other pharmacological activity likely to interact with THC.(16) In mice, pretreatment with CBD increased brain levels of THC nearly threefold and there is strong evidence that cannabinoids can increase the brain concentrations and pharmacological actions of other drugs.(562)

Five endogenous cannabinoids are known, of which anandamide (EAE), 2-arachidonylglycerol (2 AG), and 2-archidonyl glyceryl ether are the best characterized. There is evidence that besides the two cannabinoid receptor subtypes that have been cloned, additional cannabinoid receptor subtypes and vanilloid receptors are involved in the complex physiological

functions of the cannabinoid system that include motor coordination, memory procession, control of appetite, pain modulation and neuroprotection.(732) Evidence suggests that the physiological roles of these endocannabinoids function as diffusible and short lived intercellular messengers that modulate synaptic transmission. Recent studies have provided strong experimental evidence that endogenous cannabinoids mediate signals retrogradely from depolarized postsynaptic neurons to presynaptic terminals to suppress subsequent neurotransmitter release, driving the synapse into an altered state.(562) In hippocampal neurons, depolarization of postsynaptic neurons and resultant elevation of calcium lead to transient suppression of inhibitory transmitter release. Depolarized hippocampal neurons rapidly release both AEA and 2 AG in a Ca2+ dependent manner. In the hippocampus, cannabinoid receptors are expressed mainly by GABA (gamma amino butyric acid) mediated inhibitory interneurons. Synthetic cannabinoid agonists depress GABA release from hippocampal slices.(562) However, in cerebellar Purkinje cells, depolarization induced elevation of calcium causes transient suppression of excitatory transmitter release depolarization induced suppression of excitation.(405) Thus endogenous cannabinoids released by depolarized hippocampal neurons may function to down regulate GABA release.(405) Further, signaling by the endocannabinoid system appears to represent a mechanism by which neurons can communicate backwards across synapses to modulate their inputs.

There are two known cannabinoid receptor subtypes. Subtype 1 (CB1) is expressed primarily in the brain whereas subtype 2 (CB2) is expressed primarily in the periphery.(357,543) Cannabinoid receptors constitute a major family of G protein-coupled, 7-helix transmembrane nucleotides, similar to the receptors of other neurotransmitters such as dopamine, serotonin, and norepinephrine.(165,530) Activation of protein kinases is responsible for some of the cellular responses elicited by the CB1 cannabinoid receptor.(590)

The pharmacological properties have been extensively studied. More recently, biosynthetic pathways of many of the major cannabinoids have been successfully established.(212,629) Several biosynthetic enzymes including geranylpyrophosphate: olivetolate geranyltransferase, tetrahydrocannabinolic acid (THCA) synthase, cannabidiolic acid (CBDA) synthase and cannabichromenic acid (CBCA) synthase have been purified from young rapidly expanding leaves of cannabis sativa. In addition, molecular cloning, characterization and localization of THCA synthase have been recently reported.(629) THCA and cannabigerolic acid (CBGA), its substrate, were shown to be apoptosis-inducing agents that might play a role in plant defense. Transgenic tobacco hairy roots expressing THCA synthase can produce THCA upon feeding of CBGA.

These results establish the basic and advanced chemistry of cannabis and in the context of human pharmacology to prove that the chemistry of cannabis is known and reproducible. The next sections also discuss related issues, so some cross reference is implicit and to a certain degree repetitive as necessary to separately address each factor.

B. Medical use of cannabis is considered safe

The contemporary era of clinical research with cannabis began when the first FDA-approved clinical study of cannabis use in a patient population in 15 years enrolled its first

subject.(4,415) Overall, the 33 completed and published American controlled clinical trials with cannabis have studied its safety, routes of administration, and use in comparison with placebos, standard drugs, and in some cases dronabinol, in: appetite stimulation in healthy volunteers, the treatment of human immunodeficiency virus (HIV) neuropathy and other types of chronic and neuropathic pain, both pathological and experimentally induced, spasticity in multiple sclerosis, weight loss in wasting syndromes, intraocular pressure in glaucoma, dyspnea in asthma, both pathological and experimentally induced, and emesis, both secondary to cancer chemotherapy and experimentally induced. There has been a long-term, prospective, federally funded cannabis clinical study jointly administered by National Institute on Drug Abuse (NIDA) and FDA. This study has been running for over 30 years without any demonstrable adverse outcomes related to chronic medicinal cannabis use.(594) According to an explanation from the United States Public Health Service, this program was closed to new enrollees in 1992 because the government believed the program was undermining the illegal status of the substance.(556)

Wang, et al. performed a systematic review of safety studies of medical cannabinoids published over the past 40 years to create an evidence base for cannabis-related adverse events and to facilitate future cannabis research initiatives. Ultimately 23 randomized controlled trials and eight observational studies of medical cannabis were used in the analysis. In the 23 randomized controlled trials, the median duration of cannabinoid exposure was two weeks (range eight hours to 12 months). Of all the adverse events reported, 97 percent were considered “not serious,” with the most commonly reported “dizziness.” The remaining three percent that were considered serious involved relapse of multiple sclerosis, vomiting, and urinary tract infection.(714) There has never been a reported death.

The recent discovery of an endogenous cannabinoid (endocannabinoid) system with specific receptors and ligands has increased our understanding of the actions of cannabis in terms of both safety and efficacy. The endocannabinoid system, present throughout the human body, helps regulate the function of major systems in the body, making it an integral part of the central homeostatic modulatory system—the check-and-balance molecular signaling network that keeps the human body healthy. The discovery and elucidation of the endogenous cannabinoid signaling system with widespread cannabinoid receptors and ligands in human brain and peripheral tissues, and its known involvement in normal human physiology, specifically in the regulation of movement, pain, appetite, memory, immunity, mood, blood pressure, bone density, reproduction, and inflammation, among other actions, has led to the progression of our understanding of the therapeutic actions of cannabinoid botanical medicines from folklore to valid science. The endocannabinoid system represents a previously unrecognized ubiquitous network in the nervous system. There is a dense receptor concentration in the cerebellum, basal ganglia, and hippocampus, accounting for the effects on motor tone, coordination and mood state.(14,15,103,104,714)

There are very few cannabinoid receptors in the brainstem, which may account for the remarkably low toxicity. Recently MRI studies investigated brain morphology related to current and lifetime degree of cannabis use in long term, heavy cannabis users without intensive use of other illicit drugs. Voxel-based morphometry was used to assess differences in regional grey and white matter volume between 33 heavy cannabis users and 42 matched controls.(148) Grey and white matter volume analyses showed that regional grey matter volume in the anterior

cerebellum was actually larger in heavy cannabis users.(148) Gray matter is the cortex of the brain which contains nerve cell bodies and appears gray in color. White matter is the part of the brain that contains myelinated nerve fibers. It is called white matter because the color of myelin appears white. In essence, gray matter is the functional brain tissue, and white matter is the supporting structure. Volume changes appeared to be focused in the orbitofrontal cortex, anterior cingulate cortex, striatum, amygdala, hippocampus, in addition to the cerebellum. These are all regions known to be high in CB1receptor concentrations. No associations were found between white matter volume and measures of cannabis use or dependence. However, the clinical implications of this are not known. There are very few studies done examining cannabis abuse in relation to brain structure and the results have been variable and inconsistent. This likely reflects differences in methodology of imaging, as well as the degree of cannabis abuse, and the concomitant use of other substances.

i. The safety of cannabis: cannabis has never caused a lethal overdose (LD50 standard)

There has never been a lethal overdose of marijuana reported in humans.(16,509) In clinical pharmacology, a lethal dose (LD) 50 is the most commonly used indicator for the toxicity of a drug. The LD50 is the dose at which 50 percent of subjects who ingest this drug will die. There is no known LD50 for any form of cannabis or any cannabinoid based medicine.(105) In its 4,000+ years of documented use, there is no report of death from overdose with cannabis.(31,106,107) If a very large dose of cannabis is consumed ("over dose"), which typically occurs via oral ingestion of a concentrated preparation of cannabis flowers' resin (e.g., in the form of an alcohol tincture or lipophillic extract), agitation and confusion, progressing to sedation, is generally the result.(443) This is time limited and disappears entirely once the cannabis and its psychoactive components are fully metabolized and excreted. This usually occurs within three-to-four hours, although oral ingestion may prolong the duration of these effects.

ii. Cannabis is safer than current, legal Schedule II opiate drugs

Contrast the remarkable safety of cannabis with the equally remarkable toxicity of opioids. As little as two grams of dried opium poppy sap (roughly 200 mg morphine sulfate) can result in death in an average size human (70 kilogram male) due to profound respiratory suppression.(702)

This growing documentation of usefulness and safety of cannabis comes at a time when there have been near epidemic increases in deaths related to prescription opioid analgesics.(134,145,229,230,341,520,527,618,639,640,740) A number of studies have now clearly linked risk of fatal and nonfatal opioid overdose to prescription use, with the risk increasing with the prescribed dosages.(134,618,537) According to the Centers for Disease Control and Prevention (CDC), from the years 1999 through 2006, the number of prescription opioid poisoning deaths in the United States (US) nearly doubled, from approximately 20,000 to 37,000.(116) This increase coincided with a nearly fourfold increase in the use of prescription opioids nationally.

iii. History of cannabis evidences safety

Cannabis was criminalized in the 1930s, and against the advice of most major medical societies, the use of cannabis for any purpose, including medicinal, was criminalized in the United States by 1942.(307, 435,478) Prior to this, there were many cannabis-based prescription medications commercially manufactured by companies including Eli-Lilly, Parke Davis, and Sharp Dohme (now Merck Sharp Dohme).

Thus, over the past decades there have been further developments in opioid-based medicines while research in cannabinoid-based medicines was significantly slowed down. Today there are a multitude of opioid medicines widely available, in pills, patches, as well as for injection, inhalation, and implantation. The only form of a DEA-approved cannabinoid based medicine available in the United States is dronabinol (Marinol). According to research, potentially much of the morbidity and mortality caused by opioid toxicity over the past 70 years could have been reduced or prevented if cannabis had remained available on the United States pharmacopeia to serious illnesses.(35,37)

iv. The side effects of cannabis are milder than the other Schedule II drugs

As with any drug, cannabis is not without side effects. A patient does not need to be intoxicated to get a beneficial medical effect.(102) Cannabis may induce euphoria and, as such, may be psychologically addictive, but much less so than other Scheduled II drugs. There is no severe physical withdrawal syndrome associated with cannabis.(18,20) Cannabis addiction is amenable to treatment.(102) Cannabis may induce paranoia and disorientation, particularly in novice users, but again, less so than other Schedule II drugs.(11)

Many of the undesired psychoactive effects of cannabis are due to THC, which is among the reasons that dronabinol is not a suitable alternative (because dronabinol is 100 percent THC as opposed to natural cannabis which is only 15 percent THC).(11) However newer medicinal strains of cannabis are lower in THC and higher in the non-psychoactive, more therapeutic cannabinoids, such as CBD, and CBN. These compounds further improved the efficacy of cannabis.(18)

C. There are adequate and well-controlled studies proving the medical efficacy of cannabis

Regarding the degree and adequacy of well-controlled studies proving efficacy of cannabis as medicine, a review of the current scientific evidence is provided herein, followed by historical and societal perspectives. Regarding the accessibility and availability of these studies, all of the research studies cited herein, are available on the National Library of Medicine/PubMed (http://www.ncbi.nlm.nih.gov/pubmed).

i. Review of the current scientific evidence proves the medical efficacy of cannabis

Four reviews of modern human clinical studies with cannabis and cannabinoids in the United States and elsewhere have recently been published in peer-reviewed literature. (49,197, 471,569) Musty et al. reviewed seven state health department-sponsored clinical trials with data

from a total of 748 patients who received a dose of cannabis and 345 patients who received oral THC for the treatment of nausea and vomiting following cancer chemotherapy in Tennessee (1983), Michigan (1982), Georgia (1983), New Mexico (1983 and 1984), California (1989), and New York (1990).(471) To assess the evidence from these clinical trials, the authors systematically performed a meta-analysis of the individual studies, to assess possible beneficial effects. These trials were randomized, although it is not clear that they were truly blind. The authors found that patients who received a dose of cannabis experienced 70-100 percent relief from nausea and vomiting, while those who used oral THC experienced 76-88 percent relief.(471) Even judged using the strictest of evidence-based medicine (EBM) criteria, the evidence is convincing that cannabis does relieve nausea and vomiting in this setting. Bagshaw, et al. performed a systematic, comprehensive review of 80 human studies of cannabis and cannabinoids, and found similar conclusive evidence in support of cannabis use in the treatment of refractory nausea and appetite loss resulting from cancer treatment.(35)

Ben Amar et al., performed a meta-analytic review of all articles published on Medline and PubMed from inception of up till July 1, 2005.(49) The key words used were cannabis, marijuana, marihuana, hashish, hashich, haschich, cannabinoids, tetrahydrocannabinol, THC, dronabinol, nabilone, levonantradol, randomised, randomized, double-blind, simple blind, placebo-controlled, and human. The research also included studies published in English, French, and Spanish. For the final selection, the authors only included properly controlled clinical trials. Open label studies were excluded. Seventy-two controlled studies evaluating the therapeutic effects of cannabis and cannabinoids were identified. The forms of cannabis and approximate dosages were included as well as efficacy, and adverse effects. The authors concluded that on the basis of the reviewed studies, cannabinoids present significant therapeutic potential as antiemetic, appetite stimulants, analgesics, and also shows significant benefit in the treatment of multiple sclerosis, spinal cord injuries, Tourette's syndrome, epilepsy, and glaucoma.(49)

Rocha et al. performed a systematic review and metaanalysis identified 30 randomized, controlled clinical trials that evaluated the antiemetic efficacy of cannabinoids in comparison with conventional drugs and placebo.(569) A Cochrane-style meta-analysis of 18 studies, including 13 randomized, controlled clinical trials comparing cannabis to standard antiemetics for treatment of nausea and vomiting in cancer patients receiving chemotherapy, revealed a statistically significant patient preference for cannabis or its components versus a control drug, the latter being either placebo or an antiemetic drug such as prochlorperazine, domperidone, or alizapride.(49)

ii. Medicinal dosing paradigms are safe and effective and alternatives to smoking are recommended

Dosing paradigms for medicinal cannabis have been previously described.(16,105) With simple trial and error, most patients are able to get the right combination of cannabinoids that will address their symptoms and meet their needs. While research has not shown cannabis smoke definitely causes lung cancer, it can irritate bronchial mucosal membranes.(37,340)

In any case, cannabis does not need to be smoked to be effectively used as medicine. Cannabis can be vaporized. Cannabinoids are volatile and will vaporize at temperatures in the range of 250 degrees Fahrenheit, much lower than actual combustion.(193,438,698) Heated air

is drawn through cannabis and the active compounds vaporized, which are then inhaled. This rapid delivery of the cannabinoids allows for easy titration to desired effect, much as with smoking yet without health risks.(87,374,428) Additionally, cannabis can be ingested orally, or applied topically in a liniment.(105)

iii. Many known cannabinoids (not including THC) have therapeutic value with little or no cognitive or psychoactive side-effects; dronabinol (Marinol) is not an appropriate substitute for cannabis due to its 100 percent THC and lacking therapeutic cannabinoids

There are many known cannabinoids in the cannabis plant that have tremendous therapeutic value, yet have little or no cognitive or psychoactive effects.(11,18,102) The cannabinoids are lipophilic, 21 carbon terpenes, and include delta-9 THC and delta-8 THC, of which the THC produces the majority of psychoactive effects.(679) While the DEA considers cannabis a Schedule I drug, it classifies dronabinol (Marinol) as Schedule III. Dronabinol is 100 percent THC and is potentially very psychoactive. Natural cannabis typically would be no more than 15 percent THC by weight. Thus it is inconsistent that cannabis, with 15 percent THC, remains a Schedule I drug, while dronabinol, at 100 percent THC, is Schedule III.

In addition, many patients find dronabinol too sedating and associated with too many psychoactive effects due to its 100 percent THC. Dronabinol is not an appropriate substitute for natural cannabis because other major cannabinoids include cannabidiol (CBD) and cannabinol (CBN) in the natural substance, both of which significantly modify the effects THC and have distinct therapeutic and advantageous effects of their own. CBD appears to modulate and reduce any untoward effects of THC.(72,87,339,374,428,462,595,746) CBN appears to have distinct pharmacological properties that are quite different from cannabidiol.(72) CBN has significant anticonvulsant, sedative, and other pharmacological activities likely to interact with the effects of THC.(72) CBN may induce sleep and may provide some protection against seizures for epileptics.(339) Of relevance for pain management for serious illnesses, in addition to analgesia, the following dose-dependent pharmacologic actions have been observed in studies: muscle relaxation, anti-inflammatory effects, neuroprotection in ischemia and hypoxia, enhanced well-being, and anxiolysis.(16) The ratios of the various cannabinoids differ according to the plant strain, and, to some extent, how the plant is grown.(678)

Sharing Schedule I with cannabis are heroin, lysergic acid, and methamphetamine. Schedule II is a category of drugs considered to have a strong potential for abuse or addiction, but that also have legitimate medical use. Included here are opium, morphine, cocaine, and oxycodone. Schedule III drugs are felt to have even less abuse or addiction potential than Schedule I or II drugs and have a beneficial medical use. Included here are dronabinol, hydrocodone, amphetamine-based stimulants, and short-acting barbiturates. Schedule IV and V drugs are felt to have even less risks. Schedule IV drugs include benzodiazepines, while Schedule V drugs include antidiarrheals and antitussives that contain opioid derivatives. For further perspective, the DEA does not schedule carisoprodol (Soma) at all, implying that this agency does not consider it a dangerous drug. Carisoprodol is a widely used muscle relaxant whose active metabolite is the barbiturate meprobamate. Carisoprodol also shows serotonergic activity at higher levels and has produced overdose in humans. Abrupt cessation in patients taking large doses of carisoprodol will produce withdrawal, characterized by vomiting, insomnia,

tremors, psychosis, and ataxia. Given that dronabinol, being 100 percent THC and highly psychoactive, is Schedule III, and the potentially addictive drug carisoprodol is unscheduled, it is inconsistent that cannabis remains a Schedule I drug. Schedule II is entirely appropriate for cannabis.

Potential analgesic sites of action for cannabinoids have been identified at brain, spinal cord and peripheral levels.(87,374,428,595) There is strong data indicating that neurons in the rostroventral medulla and periaqueductal grey are involved the brain-mediated analgesic effects of cannabinoids.(213) There are also spinal mechanisms of analgesia, including cannabinergic inhibition of gamma amino butyric acid (GABA), glycine, and glutamate release. (122, 226, 304, 305, 464, 600, 636) There is also a growing body of evidence showing a peripheral analgesic action of cannabinoids, particularly if inflammation is present.(196,688) Animal studies have demonstrated analgesic effects of locally delivered cannabinoids at doses that would not be systemically effective.(196) The mechanisms of these peripheral analgesic actions are not completely understood but appear to be related to the anti-inflammatory effects of cannabinoids. Cannabinoids have profound effects on cytokine production, although the direction of such effects is variable and not always mediated by cannabinoid receptors. Another proposed mechanism for the anti-inflammatory actions is cannabinoid-induced increased production of eicosanoids that promote the resolution of inflammation. This differentiates cannabinoids from cyclooxygenase-2 inhibitors that suppress the synthesis of eicosanoids that promote the induction of the inflammatory process.(16,35)

D. Cannabis has been accepted by the medical community as meeting the current, modern accepted standards for what constitutes medicine

On November 10, 2009, the American Medical Association (AMA) voted to reverse its long-held position that cannabis remain a Schedule I substance. The AMA adopted a report drafted by the AMA Council on Science and Public Health (CSAPH) entitled, “Use of Cannabis for Medicinal Purposes,” which affirmed the therapeutic benefits of marijuana and called for further research. The AMA CSAPH report concluded that, “short term controlled trials indicate that smoked cannabis reduces neuropathic pain, improves appetite and caloric intake especially in patients with reduced muscle mass, and may relieve spasticity and pain in patients with multiple sclerosis.” Furthermore, the report urges that “the Schedule I status of marijuana be reviewed with the goal of facilitating clinical research and development of cannabinoid-based medicines, and alternate delivery methods.”

The AMA’s position change on medical cannabis followed a resolution adopted in 2008 by the American College of Physicians (ACP), the country’s second largest physician group and the largest organization of doctors of internal medicine. The ACP resolution also called for reconsideration of moving medicinal cannabis out of schedule I after performing an “evidence-based review of the current science” on the medical efficacy of cannabis, which this report provides in part.

The Institute of Medicine (IOM), a very prestigious organization of clinical and basic science researchers, was among the first major physician based group to adopt a new stance, issuing the landmark publication, “Marijuana and Medicine” on April 7, 2003. This consensus

report addressed the scientific basis and the therapeutic effects of cannabis to treat a multitude of medical conditions. The IOM consensus book specifically evaluates how well cannabis meets all of the current, modern accepted standards for what constitutes "medicine." This document is available on the IOM website: http://iom.edu/Reports/2003/Marijuana-and-Medicine-Assessing-the-Science-Base.aspx

There is now consensus of medical opinion concerning medical acceptability of cannabis among the largest groups of physicians in the United States. The medical community has increasingly recommended cannabis as an accepted form of therapeutic medicine for multiple serious illnesses. Members of the medical community have adopted effective treatment protocols for certain conditions. The medical community continues to develop methods of safe, consistent and effective dose and potency customized to individual patients' needs.

Much research as described throughout this report has proven cannabis' effectiveness, and allowing patients to access and use cannabis for medical use consistently enjoys widespread support among clinicians. The available medical research indicates that cannabis is highly effective in treating a number of problems commonly encountered in medicine. Arguably, to reclassify it, only one accepted treatment modality is necessary: for example, treatment for neuropathic pain and wasting associated with HIV/AIDS, which is undisputable among any physician across the United States—that alone provides sufficient justification to reclassify cannabis for medical purposes. Many patients who are currently on long term opioids could potentially be treated with either cannabis alone or in combination with a lower dose of opioids (instead of far more harmful long-acting opioid medication).

From a pharmacological perspective, cannabinoids are considerably safer than opioids and have broad therapeutic applicability. Cannabis is a medicine that has proved efficacious and could be potentially very beneficial for patients and much safer than other "legal" options such as opioid based medicines. This is an opinion that doctors share across the county. Further doctors have developed dosing and potency applicability and methods for specific patients' condition, and these methods have become accepted and more widespread across the medical community in our nation and beyond.

E. The scientific evidence is widely available

The scientific evidence is replete and widely available. As the previous sections fully elucidate, the scientific evidence supports the rescheduling of cannabis for medical use. The evidence is widely available in complete form through published journals and on the internet just like any other medicinal drugs. The evidence is far more than anecdotal self-reported effects by patients. Double-blind placebo studies have shown effectiveness following the FDA's regulations to prove drug efficacy.

i. Scientific evidence regarding the safety and efficacy of cannabis is readily available directly from the National Library of Medicine

The scientific evidence regarding the safety and efficacy of cannabis is readily available directly from the National Library of Medicine (http://www.ncbi.nlm.nih.gov/pubmed/ also known as MEDLINE(R) or PubMed Central). This is the United States government's repository

for peer-reviewed scientific research. On this website the independently peer-reviewed research papers can be identified with the abstracts of research, a summarized form of a paper published in the medical literature. The full, complete data set can be accessed from the specific journal that the work is published in. For some journals there may be a small fee required to access this unless the person accessing the journal has a subscription or works at an institution with a group subscription.

There are now considerably more randomized, double-blinded, placebo-controlled clinical trials documenting the efficacy of cannabis for medicinal treatment of any number of conditions (pain, nausea, spasticity, glaucoma) than would typically be required of a standard prescription medication to obtain FDA approval for a given purpose (especially compared with the last time the FDA reviewed the matter in 2006). This is now being documented summarily in the Cochrane Library data base as well. There are several well done Cochrane reviews that summarize the multiple controlled, large scale, clinical trials that have been conducted with cannabis for efficacy as well as safety.(14) In fact, a simple word search on PubMed using just one keyword phrase "medical marijuana" reveals more than 2,389 published papers in peer-reviewed journals. Doing a search using the keyword "hydrocodone," the most widely prescribed opioid analgesic in the United States, reveals a total of only 508 published papers (search done November 27, 2011; 12:00 PST, English language literature only): *hydrocodone is the most commonly prescribed opioid medication in the United States, and the active ingredient in Vicodin; **active opioid ingredient in Percocet®; +active opioid ingredient in tapentadol®

ii. Table One compares the number of Medline citations for medical marijuana compared to other commonly prescribed opioid medications (as of 11/27/2011; 12:00 PST):

Medication (name/search term)	Number of Medline (peer reviewed) Citations
Medical marijuana	2,389
Hydrocodone*	508
Oxycodone**	1553
Tapentadol+	81

TABLE ONE

For the purposes of example, the results of a series of randomized, placebo-controlled FDA-approved clinical trials performed by regional branches of the University of California (UC) demonstrated that inhaled cannabis holds therapeutic value that is comparable to or better than conventional medications, particularly in the treatment of multiple sclerosis. These findings were publicly presented to the California legislature, and also appear online here: http://www.cmcr.ucsd.edu/images/pdfs/CMCR_REPORT_FEB17.pdf.

Further, the UC findings paralleled those previously reported by the American Medical Association's Council on Science and Public Health. The research on medicinal cannabis is subject to all the standard procedural protocols required for all medical research. This provides ample opportunity for peer members of the scientific community to fully vet and scrutinize the data demonstrating safety and efficacy of cannabis.

With respect to the Department of Health and Human Services (HHS) regarding the five cited elements required to make a determination of "currently accepted medical use" for medical

cannabis, all of these have been fulfilled as described herein. As noted above, there is a more complete scientific analysis of the chemical components found in cannabis than in the most commonly prescribed opioid medications. In fact, there are over four times more studies assessing the efficacy and safety of cannabis for medical use than there are for hydrocodone. These studies must pass through the same vetting process as any other study published in a peer reviewed journal. In fact, the data above is from only the peer reviewed journals accepted by the National Library of Medicine, which has its own stringent criteria for citing journal articles (see: http://www.ncbi.nlm.nih.gov/pubmed).

Research on the medical use of cannabis has unmistakably progressed to the point that it can be considered to have a "currently accepted medical use" as required by 21 U.S.C. 812(b)(2)(B)).

iii. With respect to a consensus of medical opinion, currently all of the following health organizations have issued statements in favor of medical cannabis

International and National Organizations

AIDS Action Council
AIDS Treatment News
American Academy of Family Physicians
American College of Physicians
American Medical Association
American Medical Student Association
American Nurses Association
American Preventive Medical Association
American Public Health Association
American Society of Addiction Medicine
Arthritis Research Campaign (United Kingdom)
Australian Medical Association (New South Wales) Limited
Australian National Task Force on Cannabis
Belgian Ministry of Health
British House of Lords Select Committee on Science and Technology
British House of Lords Select Committee on Science and Technology (Second Report)
British Medical Association
Canadian AIDS Society
Canadian Special Senate Committee on Illegal Drugs
Dr. Dean Edell (surgeon and nationally syndicated radio host)
French Ministry of Health
Health Canada
Kaiser Permanente
Lymphoma Foundation of America
The Montel Williams MS Foundation
Multiple Sclerosis Society (Canada)
The Multiple Sclerosis Society (United Kingdom)

Exhibit B: Statement of Grounds

National Academy of Sciences Institute Of Medicine (IOM)
National Association for Public Health Policy
National Nurses Society on Addictions
Netherlands Ministry of Health
New England Journal of Medicine
New South Wales (Australia) Parliamentary Working Party on the use of Cannabis for Medical Purposes
Dr. Andrew Weil (nationally recognized professor of internal medicine and founder of the National Integrative Medicine Council)

State and Local Organizations

Alaska Nurses Association
Being Alive: People With HIV/AIDS Action Committee (San Diego, CA)
California Academy of Family Physicians
California Medical Association
California Nurses Association
California Pharmacists Association
Colorado Nurses Association
Connecticut Nurses Association
Florida Governor's Red Ribbon Panel on AIDS
Florida Medical Association
Hawaii Nurses Association
Illinois Nurses Association
Life Extension Foundation
Medical Society of the State of New York
Mississippi Nurses Association
New Jersey State Nurses Association
New Mexico Medical Society
New Mexico Nurses Association
New York County Medical Society
New York State Nurses Association
North Carolina Nurses Association
Rhode Island Medical Society
Rhode Island State Nurses Association
San Francisco Mayor's Summit on AIDS and HIV
San Francisco Medical Society
Vermont Medical Marijuana Study Committee
Virginia Nurses Association
Washington State Medical Association
Washington State Pharmacy Assocaition
Whitman-Walker Clinic (Washington, DC)
Wisconsin Nurses Association

2. OTHER CURRENT SCIENTIFIC KNOWLEDGE (FACTOR THREE)

The third factor the Secretary must consider is the state of current scientific knowledge regarding cannabis. Thus, this section, in combination with the previous pharmacology section, discusses the chemistry, human pharmacokinetics, and medical uses of cannabis. In addition, there are a multitude of new randomized, controlled clinical trials using cannabis that have been published in the past five years, which are new since the previously cited (FDA 2006 report) metanalyses.(5,6,7,35,143,197,280,281,471,711) These investigations were done primarily in HIV-related painful neuropathy, spasticity in multiple sclerosis (MS), and appetite stimulation in HIV patients.

All of these recent studies have shown statistically significant improvements in pain relief, spasticity, and appetite in the cannabis-using groups compared with controls.(5,6,7,35, 143,197,280,281,471,711) A very recent systematic review and meta-analysis was done to evaluate the clinical effectiveness of analgesics in treating painful HIV-related sensory neuropathy (HIV-SN).(198) The Medline, Cochrane central register of controlled trials (www.clinicaltrials.gov, www.controlled-trials.com and the reference lists of retrieved articles) were all searched for prospective, double-blinded, randomized controlled trials investigating the pharmacological treatment of painful HIV-SN with 44 studies identified, 19 were RCTs. Of these, 14 fulfilled the inclusion criteria. Interventions demonstrating greater efficacy than placebo were cannabis, topical capsaicin, and recombinant human nerve growth factor (rhNGF), and of those three, cannabis had the strongest overall beneficial clinical effect. No superiority over placebo was reported in RCTs that examined amitriptyline, gabapentin, pregabalin, prosaptide, peptide-T, acetyl-L-carnitine, mexilitine, and lamotrigine.(198)

While nearly all of the published controlled clinical trials with cannabis conducted in the United States have shown statistically significant and measurable benefits in subjects receiving the treatment, there have been negative results.(121,198,299,536) Most notable perhaps was a study done by Greenberg, et al, in which 10 patients with spastic multiple sclerosis and 10 healthy controls showed a clinical improvement in pain and spasticity in some patients, but impairment in posture and balance was noted in the MS group.(299) Another study in 18 healthy females using a cannabis extract did not show an affect on heat pain thresholds in a sunburn model, but this hyperalgesia effect had not been previously seen nor has this been substantiated by another study.(563)

The vast majority of modern research indicates that cannabis has significant therapeutic efficacy in the treatment of a wide range of clinical applications. These include relief of pain associated with serious illnesses like cancer, spasticity, anorexia, nausea, glaucoma, and movement disorders. In addition, an emerging body of research suggests that the medicinal properties of cannabis may help the body in the setting of neurodegenerative disorders including ALS, Parkinson Disease, among others, as well as help against some types of malignant tumors.(3-5,13-16,30,31,37,72,102-109,122)

3. CANNABIS IS NOT AN IMMEDIATE PRECURSOR TO A CONTROLLED SUBSTANCE (FACTOR EIGHT)

The eighth factor the Secretary must consider is whether cannabis is an immediate precursor of a controlled substance. Cannabis is not an immediate precursor of another controlled substance. It is a controlled substance, and it would not metabolize into another controlled substance. Nothing more is required to address for this factor.

4. ACTUAL AND POTENTIAL FOR ABUSE (FACTOR ONE)

Generally, this factor (actual and potential for abuse) is similar to and best read together with the following sections that discuss the other factors required for this rule-making petition (dependence liability; pattern of abuse; and scope, duration and significance of abuse). The organization of this report reflects this grouping, while addressing each required factor independently for purposes of ensuring full analysis and compliance with the rule-making petition requirements.

This section discusses the issues involved with drug abuse, and begins with a review of the distinctions between the terms "addiction," "compulsive use," "abuse," "dependence," and "problems." These terms and related clinical and social concepts have evolved over time such that views of what was addiction a few decades ago no longer are the same in the general medical community today.

A. Background: definitions

Some researchers claim that cannabis is not particularly addictive. Experts assert that cannabis's addictive potential parallels caffeine's.(200,228) Hilts (1994) asked two prominent drug researchers to rank features of six common drugs: nicotine, caffeine, heroin, cocaine, alcohol, and cannabis.(200) Both experts ranked cannabis last in its ability to produce withdrawal, tolerance, and dependence. Another study had experts rank 18 drugs on how easily they 'hook' people and how difficult they are to quit. Cannabis ranked 14th, behind the legal drugs nicotine (ranked first), alcohol (ranked 8th), and caffeine (ranked 12th). (See chart in section C of this factor regarding "Addictiveness Ratings for Drugs of Abuse").

The results above reflect expert opinions. Other evidence also suggests that marijuana is not particularly addictive. For example, only a fraction of those who try cannabis eventually use it regularly. Nevertheless, some users still develop troubles related to the drug, and many request assistance in limiting their consumption.(573) In the face of these problems, the low ratings of addictive propensity seem confusing. This confusion may arise from diverse meanings for the word addiction.

The term 'addiction' developed to describe the repetition of a habit. Addiction initially did not necessarily involve drugs. Its Latin root, 'addictus,' means state, proclaim, or bind. The origin suggests an obvious, stated connection between addicted people and their actions. The word connotes surrender, and implies that an activity or substance has bound the person.(383) Addiction was usually treated as a bad habit, similar to biting one's nails compulsively. At the

beginning of the 20th century, at least in America, the term changed from a description of actions to a medical condition. This distinction may seem subtle, but converting a bad habit into a physiological disorder brings it into the domain of medical intervention. This medical approach implies that addiction is not just a troublesome activity; it is a personal condition. Medicine has transformed many troubling behaviors into biological illnesses, with many repercussions, including inconsistent and unclear clinical meaning.(225,671)

Some medical texts support the term 'addiction' as the proper expression for drug problems. This definition emphasizes preoccupation with the substance, compulsive use, and frequent relapses. People who spend considerable time and effort trying to obtain the drug appear preoccupied.

Compulsive use describes the subjective sense that one is forced to consume the drug. It need not mean intoxication at every moment. Compulsive use also can include consistent consumption under identical circumstances, such as using a drug at the same time each evening. Repeated use despite attempts to stop also typifies this definition of addiction. Proponents of this approach to defining problems emphasize loss of control. Loss of control implies that the initial use of the substance impairs the ability to stop. A tacit assumption in some medical settings suggests that these symptoms arise from a biological process, an interaction of a foreign chemical with internal physiology.(453) This approach may have inspired the disease model of addiction.

B. Background: the disease model of addiction

The disease model generates considerable emotion in many who investigate, treat, or experience drug problems. The controversy surrounding the model reflects the history of human reactions to personal difficulties as a moral issue or a moral model of addiction.

The moral model attributed troubles to ignoble thoughts, actions, or character. Some adherents to the moral model suggested that those with drug problems were weak-willed. The moral approach identified the initial source of the disorder as being inside the individual.

A shift to use of a disease model asserted that drug problems served as symptoms of an illness. This illness led people, through no fault of their own, to the problematic consumption of substances. The disease model minimized blaming addicts for symptoms beyond their control (e.g., few people fault people for contracting a disease like anthrax or influenza). No one tells people with these diseases to 'use willpower' to combat symptoms, whereas some believe resolving drug problems is a matter of willpower. The disease model suggests that condemnation wastes effort that could be better spent on therapy. This model underlies one of the most popular approaches to substance abuse treatment, the 12-step program.

Critics of the disease model suggest that viewing drug problems as a disease can have drawbacks. In an effort to minimize blaming people for addictive behavior, proponents of the disease model may have created another set of problems. The definition of disease has grown slippery. Addiction may not qualify because it does not parallel other illnesses. No bacteria or viruses lead to substance abuse the way they create anthrax or HIV/AIDS. Genes do not cause addiction in the direct way they produce Down Syndrome or hemophilia. The symptoms of

cancer do not flare up in certain environments the way that craving for liquor may increase in certain contexts. Despite these facts, some advocates of the disease model treat addiction as a purely biological phenomenon. This emphasis on biology can exclude important economic, societal, and psychological contributors.(524)

The opinion that drug problems reflect a medical disorder has certain drawbacks. The idea ignores social aspects of addiction, creates a dependence on medical treatments, and may lead to higher rates of relapse. Viewing addiction as a purely biological phenomenon minimizes established links between social class and drug problems.(34,448) This approach may blind people to the potential for limiting drug problems through social change. A purely biological approach may also lead people to rely inappropriately on medications rather than psychological treatment. Changing personal behavior is often difficult. Changing societal and cultural mores can prove even tougher. Prescribing medication for a disease is often more straightforward. The disease model also may contribute to higher rates of relapse because of a central idea about loss of control. A belief in this symptom, which describes an inability to use a drug in small amounts, may actually increase relapse rates.(419, 524)

Increases in the risk of relapse may serve as a prime example of a drawback associated with the disease model. Problem users frequently report that initial consumption of a drug invariably leads to using markedly more than they ever intended. Many assumed that a chemical process associated with the experience of intoxication impaired their ability to stop consumption. This loss of control became synonymous with addictive disease. Yet, alcoholics surreptitiously given alcohol do not show signs of uncontrolled drinking. In contrast, alcoholics who believe they have consumed alcohol after drinking a placebo do show less control over their drinking.(419) These results suggest that what people think is more important than what they consume.

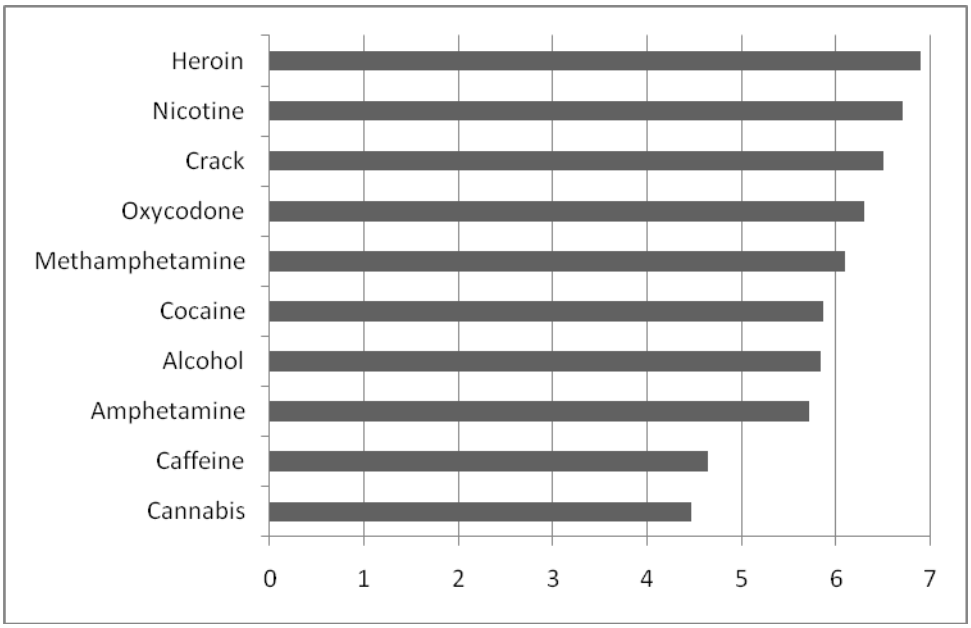
In one relevant study, cannabis users in treatment reported about their relapses. Some used on a single occasion, considered it a ‘slip,’ and returned to abstinence quickly. Others considered the single use a sign of weak will or disease and ended up consuming markedly more.(651) These data suggest that this sort of loss of control likely arises from a psychological rather than a biological process. Many researchers view these data as evidence against the disease model.

Other definitions of both addiction and disease have added to the controversy. Peele emphasizes tolerance, withdrawal, and craving as essential to addiction.(524) His work returns to the old definition of addiction, which can include actions that do not require chemicals. He extends the concept beyond drugs to nearly every behavior imaginable.(523) Yet he remains one of the most outspoken critics of the disease model. Tolerance, withdrawal, and craving all vary with features of the environment, suggesting that more than biology contributes to addictive behavior. Peele (1998) asserts that this evidence helps discredit the disease model. Other researchers argue that Peele misunderstands addiction.(710) The word may have so many different uses that it has lost its meaning. Thus, other terms have developed to describe trouble with drugs.

Because many define addiction quite broadly and disparately, some mental health professionals prefer the terms 'dependence' and 'abuse.' Others see these words as pejorative and judgmental compared to 'addiction.'(453) Oddly enough, the World Health Organization (WHO) proposed the word 'dependence' to avoid the derogatory aspects of the word 'addiction.'(195) Addiction may imply a purely physical, biological process that might neglect psychological contributors to drug problems.(245) Other terms have developed to focus on the observable behavior without hypothesizing an internal process or disease.

The foregoing discussion and debate provides background for the remaining discussion on this and the following three factors. In the end, regardless of the term applied or the clinical definition used, cannabis use, abuse, misuse, or dependence is within reasonable levels, especially as compared to other Schedule II drugs.

C. Cannabis use indicates a lower likelihood of addiction and abuse potential as compared to other substances (Table 2):



Addictiveness Ratings for Drugs of Abuse from 746 Drug Professionals.(250)

A survey of 746 mental health professionals and addictions researchers asked them to rate the addictiveness of various drugs on a seven-point scale with seven standing for extremely addictive. Participants included members of the National Association of Alcoholism and Drug Abuse Counselors, authors of papers published in peer-reviewed journals on substance abuse, and psychologists, social workers, licensed substance abuse counselors, and psychiatrists. The sample was evenly split among men and women. As the figure reveals, these experts rated licit and illicit drugs as more addictive than cannabis, with caffeine, amphetamine, alcohol, cocaine, methamphetamine, oxycodone, crack cocaine, nicotine and heroin receiving significantly higher scores. Effect sizes ranged from .18 standard deviations for caffeine to 1.53 standard deviations for heroin.

5. PSYCHIC OR PHYSIOLOGIC DEPENDENCE LIABILITY (FACTOR SEVEN)

Focusing on observable behavior has been a recurring theme for the Diagnostic and Statistical Manual (DSM) developed by the American Psychiatric Association (APA). This book attempts to define all psychiatric illnesses. Dependence and abuse appear in this work; addiction does not. Their definitions have gone through many revisions, and probably will continue to do so. The first version of the manual (the DSM I) appeared in 1952 (26); it is now in its fourth edition. Originally, the opinions of many mental health professionals contributed to the definition of any disorder. Gradually, researchers attempted to clarify the diagnoses based on science rather than opinion. Early versions of the dependence diagnosis simply required 'evidence of habitual use or a clear sense of need for the drug.'(27) This definition proved too subjective to diagnose reliably. Current definitions focus on a maladaptive pattern of use that leads to impairment or distress. Other symptoms are required for the diagnoses, as described below.

A. Cannabis has low relative dependence risk and does not reach the severity associated with other drugs

The DSM-IV defines drug dependence as a collection of any three of severe symptoms. All must create meaningful distress and occur within the same year. The diagnosis requires a certain amount of judgment on the clinician's part, but the symptoms tend to be obvious. Each symptom reflects the idea that a person requires the drug to function and makes maladaptive sacrifices to use it. The current diagnosis focuses on consequences, not the amount or frequency of consumption. In contrast, earlier versions of the DSM once employed the frequency of intoxication as a symptom. For example, the diagnosis of a disorder known as 'habitual excessive drinking' required intoxication 12 times per year.(27) This approach proved inexact, and failed to relate to the magnitude of difficulties. Thus, current diagnoses of drug dependence focus on negative consequences. They include tolerance and withdrawal, which were once considered the hallmarks of dependence. The additional symptoms are: use that exceeds initial intention, persistent desire for the drug or failed attempts to decrease consumption, loss of time related to use, reduced activities because of consumption, and continued use despite problems.

Tolerance is one of the hallmarks of physiological dependence. It occurs when repeated use of the same dose no longer produces as dramatic an effect. This symptom can indicate extensive use, and may motivate continued consumption. People do not grow tolerant to a drug, but to its effects. After repeated use, some of the effects of a drug may decrease while others may not. Tolerance to the desired effects of cannabis may encourage people to use more. Many people report using cannabis to enhance their moods.(628) Yet, tolerance develops to the mood-enhancing effect of THC.(278) This tolerance may lead people to use more to achieve the same emotional reactions. The increased use may coincide with a greater chance for problems. Ironically, tolerance to negative effects may also encourage more consumption. For example, using marijuana creates dry mouth, but this effect diminishes with use.(719) This negative effect may have inhibited use initially. People might stop using if their mouths became too dry. But once tolerance develops, their mouths do not grow as dry and they may use more. Thus,

tolerance to marijuana's effects may lead to increased consumption, and serves as a symptom of dependence.

The second symptom of dependence is withdrawal. Withdrawal refers to discomfort associated with the absence of the drug. Many drugs produce withdrawal, including the most common ones: caffeine, nicotine, and alcohol. The most notorious drug withdrawal may come from heroin. This opiate has a reputation for producing dramatic withdrawal symptoms. No two people experience withdrawal in the exact same way. Many assert that cannabis does not produce any withdrawal at all. It certainly does not create the dramatic symptoms characteristic of alcohol or heroin, and many users do not experience any problems after discontinuing use.(609) Nevertheless, people who are given synthetic THC for a few consecutive days report negative moods and disturbed sleep after they stop taking the drug.(278) People who use cannabis a few days in a row report more anxiety without the drug.(279) Cannabis can lead to withdrawal, and thus dependence, but it does not reach the severity of dependence associated with other drugs like alcohol or opiates.

The lack of flagrant, obvious cannabis withdrawal symptoms inspired the American Psychiatric Association to distinguish between types of dependence. Early versions of the diagnosis of dependence specifically noted that cannabis might cause problems in individuals who do not experience withdrawal.(14,27) The DSM-IV distinguishes between dependence with and without a physiological component. If tolerance or withdrawal appear among the three required symptoms, a diagnosis of physiological dependence is appropriate. Nevertheless, even without tolerance or withdrawal, individuals may receive a diagnosis of substance dependence without a physiological component. If they show three other symptoms, they will still receive the diagnosis. This change in procedure has made the diagnosis of marijuana dependence potentially more common.

A third symptom of dependence involves use that exceeds initial intention. This symptom suggests that individuals may plan to consume a certain amount of a drug, but once intoxication begins, they use markedly more. Use that exceeds intention was once known as loss of control. Many people misinterpreted the idea of loss of control, suggesting it meant an unstoppable compulsion to use the entire drug available. Use that exceeds intention specifically does not imply this dramatic, unconscious consumption. This symptom simply suggests that dependent users may have trouble using a small amount if they intend to.

Dependence also includes a fourth symptom: failed attempts to decrease use, or a constant desire for the drug. An inability to reduce drug consumption despite a wish to do so certainly suggests that the drug has altered behavior meaningfully. Yet, someone with no motivation to quit would likely never qualify for a failed attempt. Thus, people who have not attempted to quit may still qualify for this symptom if they show a persistent, continuous craving for the drug. An inability to stop or a constant desire suggests dependence.

A fifth symptom of dependence involves loss of time related to use. The time lost can be devoted to experiencing intoxication, recovering from it, or seeking drugs. Because marijuana is illegal, users may spend considerable time in search of it. People addicted to caffeine, nicotine, or alcohol may prove less likely to lose time in search of these substances. The number of hours

required to qualify for a meaningful loss of time is unclear, making this symptom seem subjective. Clear-cut cases include anyone whose day is devoted to finding drugs, getting intoxicated, and recovering. Anyone who spends a few hours each day on these activities would also qualify, depending on circumstances. In contrast, individuals who use cannabis for medical purposes would see increased productivity and might argue that they have lost little time in comparison with the medical benefits, so they would not likely qualify for this symptom. However, the subjective assessment of a meaningful amount of time may contribute to problems with the diagnosis of dependence.

The sixth symptom of dependence is reduced activities because of drug use. This symptom focuses on work, relationships, and leisure. The presence of this symptom suggests that the drug has taken over so much of daily life that the user would qualify as dependent. Any impairment in job performance because of intoxication, hangover, or devoting work hours to obtaining drugs would qualify for the symptom. Anyone who misses work habitually might qualify for reduced activities. Sufficient functioning at work, however, does not ensure against dependence. Even with stellar job performance, impaired social functioning can also indicate problems. If a user's only friends are also users and they only socialize while intoxicated, the substance has obviously had a marked impact on friendships. Recreational functioning is also important to the diagnosis. A user who formerly enjoyed hiking, reading, and theatre, but now spends all free time intoxicated would qualify for the symptom. This approach to the diagnosis implies that cannabis users who are not experiencing a multifaceted life can improve the way they function by using less, but it would not suggest that a medical cannabis user who improves performance would qualify.

The last symptom of dependence requires continued use despite problems. People who persist in using the drug despite obvious negative consequences would qualify for this symptom. Recurrent use regardless of continued occupational, social, interpersonal, psychological, or health trouble obviously shows dependence. Continued consumption in the face of conflicts with loved ones, employers, and family might qualify for this symptom. This creates an odd diagnostic situation because the symptom may vary with the person's environment. These interpersonal conflicts may arise from different interpersonal situations. This situation supports the idea that anyone who continues to use despite negative consequences must have a strong commitment to the drug, but members of a drug-oriented subculture might be less likely to be diagnosed with this symptom. Other problems need not involve people in the user's life. For example, anyone with emphysema who continues smoking tobacco would qualify for this symptom. People who report guilt or a loss of self-respect because of their drug use also qualify for this symptom. Those who continue using even when it leads them to have a negative view of themselves show a genuine sign of dependence. However, a medical cannabis user's quality of life would improve because of relief provided from their debilitating condition.

B. Conclusion: low risk of dependence does not reach the severity necessary to keep cannabis classified as a Schedule I substance

The seven symptoms of dependence do not indicate a risk to justify continued Schedule I placement of medical cannabis. Clearly risk is present, but it is significantly less than other legal and Schedule II drugs, especially for medical users of cannabis because performance would

likely improve in comparison with what a debilitating illness causes. Thus, reclassifying cannabis for medical use as a Schedule II is appropriate.

6. HISTORY AND CURRENT PATTERN OF ABUSE (FACTOR FOUR)

The fourth factor the Secretary must consider is the history and current pattern of abuse of cannabis. The history and current pattern of abuse can be confusing to estimate because a large percentage of United States citizens have tried marijuana at least once, but that is not as relevant to this analysis as the prevalence of use and misuse.

Some estimates suggest that over 40 percent of the nation has tried the plant. Rates were particularly high during peak eras of the 1970s.(14) For some age groups, trying marijuana is normative. For example, over 50 percent of those aged 18-25 report trying marijuana in their lifetimes, as has been the case each year from 2002-2010.(14) These reports from the National Study on Drug Use and Health (NSDUH) are available through the Substance Abuse and Mental Health Services Administration (SAMHSA) website: http://www.oas.samhsa.gov. Despite this prevalence, negative consequences remain rare. Most important, trying marijuana once should not be confused with a health problem, let alone a diagnosis of dependence or abuse.

A. Cannabis rates of dependence or abuse are remarkably low in comparison with other drugs

Rates of dependence or abuse are remarkably low. A survey of over 700 health professionals revealed that cannabis was considered less addictive than a host of other drugs, including the licit drugs alcohol, nicotine, and caffeine as well as Schedule II drugs like oxycodone, amphetamine, and methamphetamine.(250) The presence of marijuana dependence was extremely difficult to identify for many decades.(193) Recent work suggests that the diagnosis of both dependence and abuse remains extremely controversial. It is unfortunate that the term “dependence” is also used for illicit drugs with markedly more severe addictive potential and abuse dependence, including opiates. What qualifies as marijuana dependence lacks the severity and negative consequences common to dependence on alcohol or opiates.(128,193)

Even using these controversial diagnoses, rates of dependence and abuse are low. Interviews for the National Longitudinal Alcohol Epidemiologic Survey ([NLAES] and National Epidemiologic Survey on Alcohol and Related Conditions ([NESARC] each confirm that rates of dependence or abuse of cannabis have never exceed two percent in a given year.(138) These are huge studies, each with samples sizes over 40,000 people, employing extensive interviews with highly trained professionals. They likely create the most accurate estimates available. In contrast, alcohol abuse and dependence appears in seven to eight percent of the population in a given year.(138) The non-medical use of prescription drugs is markedly less common than using marijuana one time (approximately 10 percent), but over 20 percent of those people later qualify for a diagnosis of abuse.(428) Again, these SAMHSA-NSDUH reports are all available at: http://www.oas.samhsa.gov

B. Cannabis dependence causes much less severe negative consequences than other Schedule II drugs

Another important point to consider when interpreting data on marijuana problems involves a lack of focus on medical users. Currently, no large study of symptoms of dependence or abuse of marijuana focuses on patients with physician recommendations. At worst it is reasonable to generalize that if the two percent rate of dependence or abuse would generalize to medical users, then cannabis represents a far less harmful drug than other legal Schedule II substances.

One symptom of dependence involves time lost obtaining the drug. Obviously, a legitimate source of cannabis comparable to the pharmacies that provide Schedule II drugs would eliminate this symptom. In addition, given the low severity of the most common symptoms of dependence (like tolerance), it cannot be concluded that this risk always outweighs medical utility.

7. SCOPE, DURATION, AND SIGNIFICANCE OF ABUSE (FACTOR FIVE)

A subset of individuals may experience negative consequences from drugs that do not qualify for dependence but still lead to the diagnosis of substance abuse. This diagnosis requires significant impairment or distress directly related to the use of the drug. This dysfunction and strain are necessary to identify abuse. The diagnosis requires only one of the four symptoms that appear in the current criteria.(28) These symptoms include: interference with major obligations, intoxication in unsafe settings, legal problems, and continued use in the face of troubles. Each of these signs requires some interpretation on a diagnoser's part, but trained individuals apply the category reliably. Most experienced diagnosticians can agree who meets criteria for substance abuse and who does not.(694). This definition remains distinctly separate from dependence, which requires different symptoms and more of them. Although a diagnosis of abuse clearly serves as a sign of genuine troubles, many clinicians consider dependence more severe. Thus, those who qualify for dependence would not receive the less severe diagnosis of abuse.

The first symptom of abuse, interference with major obligations, requires impaired performance at work, home, or school. The idea that abuse requires interference with major obligations reflects concerns about optimal functioning. The impairment may arise because of intoxication, recovery from intoxication, or time devoted to searching for drugs. The definition is necessarily broad in order to apply to people with a variety of responsibilities. The symptom applies to employees who miss work or students who fail tests because of intoxication. One curious aspect of this symptom concerns the way some potential abusers arrange their lives to minimize the impact of their drug use on obligations. Anyone with few major obligations may become intoxicated more often or more severely without qualifying for the symptom.

The second symptom requires intoxication in an unsafe setting. The DSM specifically lists driving a car and operating machinery as hazardous situations where intoxication could create dangerous negative consequences.(632) Driving while intoxicated is unacceptable and qualifies as substance abuse.

The intoxicated performance of any task can lead to this diagnosis if impairment might create negative consequences. Driving a forklift or using power tools might qualify. Note that no negative consequences actually need to occur; their increased likelihood can qualify for abuse. Thus, those who drive intoxicated but never receive tickets or have accidents would still qualify for abuse because they have increased their likelihood of negative consequences.

The third symptom included in the diagnosis of substance abuse concerns legal problems.(76,266) The definition of this symptom makes users of legal drugs less likely to get a diagnosis of abuse than users of illegal drugs. Any arrest that arises from drug-impaired behavior, such as public intoxication or driving under the influence, clearly qualifies as abuse. Other legal problems qualify even if they do not arise from intoxication. If medical cannabis were rescheduled, the purchase and possession with the proper prescriptions would not be considered "abuse" alone, so legal problems that some individuals may currently experience should not be factored into an evaluation of the potential for abuse under the rescheduled drug.

The fourth symptom of drug abuse concerns consistent use despite problems. This symptom is identical to the last symptom of dependence (discussed under section 5. Psychic or Physiologic Dependence Liability). Note that recurrent use in the face of occupational, social, interpersonal, psychological, or health troubles qualifies as abuse. Medical use of cannabis that helps a patient withstand the effects of a serious illness, would obviously not qualify.

A. The prevalence and significance of potential abuse are limited for cannabis, especially in relation to other Schedule II substances

One of the most comprehensive studies of abuse and dependence began with interviews of over 42,000 people. This research focused on people who had used cannabis in the previous year, and revealed that 23 percent qualified for a diagnosis of abuse and six percent qualified for a diagnosis of dependence. Abuse appeared more often among rural users. Dependence appeared more often among users who were depressed.(257)

Other studies have concentrated on negative consequences rather than diagnoses. Recent, large-scale investigations focused on problems related to social functioning, health troubles, or psychological symptoms.(257) In a large sample of Americans, 85 percent of people who had used marijuana in the previous year reported none of these problems. Fifteen percent reported one, eight percent reported at least two, and four percent reported at least three negative consequences that they attributed to cannabis use. Thus, more than four out of five people who had used cannabis in the previous year reported no problems related to the drug.(482)

This information certainly helps provide estimates of marijuana problems, but the data raise questions. At first glance, it appears that 15 percent of marijuana users experience problems with the drug. However, the control group failed to account for people who did not use marijuana but also experience comparable social, medical, or psychological troubles. A meaningful control group that included people who never used marijuana would certainly help interpretations of this study. Some of the users in this study may have experienced these symptoms even if they had never used cannabis. Yet, the tacit assumption, that the cannabis

created the problems is not proved. If cannabis users reported more of these sorts of troubles than nonusers, the idea that cannabis caused the problems would be more supportable. The current approach, however, may overestimate marijuana's negative impact.

The limitations of this one study do not mean that cannabis does not cause problems. Other research supports the idea that a percentage of cannabis users experience troubles with the drug. Approximately nine percent of one group of users followed for five years developed negative consequences.(718) These researchers defined problems in four aspects of life. These included negative effects of the drug, problems controlling use, and interpersonal difficulties. They also included unfavorable opinions about use. Adverse opinions included feeling that marijuana use had grown excessive, guilt-inducing, or objectionable.

Unlike the NIDA study above, which focused on problems that could have occurred to anyone, this study identified troubles that concentrate more on marijuana. The nine percent of the sample labeled problem users experienced troubles in at least three of these domains. These studies both suggest that cannabis use is not harmless, and that some individuals experience negative consequences from the drug. Even those who may not qualify for addiction, abuse, or dependence might benefit from altering their marijuana consumption. A focus on problems may enhance the prevention of addiction, abuse, or dependence, however they are defined. However, the prevalence of associated problems is less than other legal medicine.

B. Conclusions

Cannabis is the most commonly consumed drug that is currently in Schedule I, with 200-300 million users worldwide. Approximately a third of Americans have tried the substance at least once. Less than five percent of Americans report using the drug every week. Estimating the exact number of users is difficult. The amounts that people consume are also hard to estimate. A variety of definitions of abuse and misuse of the drug exist. These include addiction, dependence, abuse, and problems. Addiction does not have a universal definition, making the term difficult to use scientifically. Abuse and dependence are diagnosed reliably and clearly can apply to problem marijuana users. Nevertheless, the abuse and dependence diagnoses may not provide the clear information one might learn from a simple list of marijuana problems. More to the point, cannabis problems are not particularly common, but six to nine percent of users report some difficulties with the drug, which is significantly less than other categories of legal Scheduled II and III drugs.

8. PUBLIC HEALTH RISK (FACTOR SIX)

This section will review and show that cannabis plays little role in producing social problems like amotivation, reckless driving, and aggression or hostility. Details of the relevant studies appear below.

A. Amotivational syndrome generally is not a dangerous side-effect, and data shows little correlation with cannabis use

Some concern has been expressed about the drug's long-term impact on motivation.(475-480) By the late 1960s, researchers coined the expression 'amotivational syndrome' to describe indifferent, apathic people who used marijuana, yet data has not proven that marijuana actually alters motivation. As a result, varied definitions and measurements of amotivational syndrome have led to some review of the concept.

To measure motivation or amotivational syndrome, some investigators have examined employment history and educational achievement, and others reviewed performance on laboratory tasks. Nearly all measurement strategies reflect generalized values about productivity. Many researchers tacitly assume that motivated people perform well in school, work hard for their employers, and persevere on laboratory tasks. Yet, there are many exceptions of the world's most famous achievers failing in these domains. People do not share all goals, or value the pursuit of objectives in the same way. Some cultures emphasize different values than others.(86)

The notion of amotivational syndrome can inadvertently pathologize behaviors that many people in other cultures find fulfilling.(467) For example, vacation time varies dramatically from country to country, reflecting different attitudes about leisure and productivity.(568) In addition, motivation and achievement do not necessarily lead to happiness or increased satisfaction in life. The idea of amotivational syndrome may present a false promise that accomplishments lead invariably to happiness.

Even within our society, the definitions of amotivational syndrome vary considerably. There is no formal diagnosis or established list of symptoms. Most researchers employ their own unique measures of motivation, making comparisons between studies difficult. Reports usually describe amotivation as a subtle shift in priorities. Achievement becomes less important; leisure becomes more important. Sufferers purportedly have few long-term goals or no concrete plans for attaining them. They may lose the ability to concentrate, endure frustration, and participate in life. Even if a cannabis-induced amotivational syndrome exists, its symptoms are far less problematic than the obvious problems associated with the abuse of other drugs. Chronic cannabis users rarely report the drastic financial, social, and occupational difficulties typical of addiction to opiates.

The purported symptoms of amotivational syndrome are hardly unique to cannabis use. Clinical depression often includes the fatigue, poor concentration, and apathy typical of amotivation. This overlap suggests that a subset of depressed people who use marijuana may

account for clinical observations of amotivational syndrome. People who are depressed or unmotivated may happen to use cannabis, giving the impression that the drug has created the symptoms. In fact, the links among depression, amotivation, and cannabis consumption are not straightforward.

Recent data reveal that cannabis consumption has no significant association with depression in adults. A subset of people who use marijuana to cope with problems show more depressive symptoms, but it is not clear that cannabis use caused their depression. People who first tried marijuana before age 16 showed more depression later in life, yet this relationship disappeared when the use of other drugs was taken into account.(261) A separate study revealed that measures of motivation correlated more with depression than with marijuana consumption, even among heavy users.(471) Thus, depression rather than cannabis may cause amotivational symptoms, and medical cannabis users feel less pain and are often less depressed as a result.

The idea that cannabis use diminishes motivation requires the same firm evidence of association, temporal antecedence, and isolation on the gateway effect. Marijuana must precede and correlate with amotivation to cause it. The symptoms also must not stem from some other contributor like personality, depression, or the use of another drug. Ensuring that amotivational syndrome arises from cannabis requires experiments. Researchers can randomly assign people to receive cannabis or placebo. This arrangement ensures that everyone is equally likely to end up in the group that uses cannabis, assuring that any identified deficits arise from cannabis rather than personality, depression, or other drug use.

In an alternative approach, participants work after use of a placebo and at other times after cannabis use. This strategy, known as a within-subjects design, ensures that all the people work both intoxicated and sober. Investigators can then compare each person's intoxicated performance to his or her own work in the absence of the drug. Under these circumstances, any identified impairment must stem from cannabis. Thus, laboratory experiments can rule out alternative explanations for the impact of cannabis on motivation. This type of research requires extensive time, effort, and funding. Cannabis use over many days should produce the lethargy and lack of ambition typical of the disorder. As the next section discusses, laboratory experiments on repeated daily exposure reveals no evidence for amotivaltional sydrome.

i. Laboratory performance does not indicate amotivational syndrome in cannabis users

In one of the first studies of chronic cannabis administration, researchers employed six men to build chairs for 70 days. They earned two dollars per chair initially, but went on strike twice and raised their fees. They had periods without cannabis, and weeks when they could purchase as much as they wanted. For 28 days the researchers required that they use at least two doses containing a total of 17 mg of THC. Generally, the men built fewer chairs and worked fewer hours when required to consume cannabis. They also built fewer chairs immediately after they went on strike and increased their wages. The men showed no other signs of amotivation.

This study supports the idea that intoxication can decrease productivity.(444) Yet, it is unclear if this would qualify as evidence for amotivational syndrome. Arranging for a strike to increase wages likely required motivation, organization, and drive. Making fewer chairs might

reflect lower motivation, but it more likely offers further evidence that intoxication impairs performance.

In another study of chronic administration, researchers paid 30 men to stay in the hospital for 94 days. They ingested no drugs for the first 11 days, used cannabis for the next 64, took a break from the drug for a week, used daily for nine more days, and then did not use the last three. They were paid for daily work on two different tasks. One required adding large numbers on a calculator. The other required answering textbook questions. Participants received ten cents for each correct answer on these two tasks. Acute intoxication and chronic exposure had no impact on any measure of performance. The men showed statistically comparable total responses, total correct responses, errors and time worked throughout the 94 day period.(135,136) These data offer no support for amotivational syndrome.

In another detailed experiment, 20 young men lived in a hospital for three months. They made belts for money, and used cannabis at various rates. The men were abstinent for certain periods, and could use as much as they chose at other times. On some days, researchers required that participants use a specific amount of cannabis, up to 30 mg of THC. Generally, the larger doses briefly reduced productivity. The men made fewer belts on days when they were forced to use high doses. People who used as much as they wanted initially performed more work than people who were forced to use larger amounts. Participants reportedly disliked the mandatory doses. Some even threatened to leave the experiment. However, over time, they developed tolerance, minimizing any effects on productivity, and they did not show overt signs of amotivational syndrome, including no decline in physical condition, personal hygiene, social functioning, or intellectual abilities. These signs remained absent even on days when the men made fewer belts.(96) Thus, the men in this study showed no symptoms of a motivational disorder. When they were required to use large doses of cannabis, they showed an initial drop in productivity, which quickly returned to normal.

The long-term studies discussed above offer little support for cannabis-induced losses of productivity. One standard way to manipulate motivation in the laboratory requires offering extra cash for good performance on tasks. In one study of marijuana's effects, researchers attempted to increase motivation and performance on simple tasks by offering financial incentives. On a reaction-time task, intoxicated people did not respond to this incentive as dramatically as the people who had not used cannabis. Offering extra money did not motivate people to react more quickly while intoxicated, but it did speed reaction times for people who were not intoxicated. The authors emphasize that this result offers little support for amotivational syndrome. Instead, these data mean that intoxicated people do not react to standard techniques for enhancing motivation.(538)

Two other studies performed in a residential laboratory revealed that intoxicated men were less likely to perform tasks that they disliked.(221-223) After using cannabis, these people spent less time on work and chores and more time on recreational activities. Articles often refer to these studies as evidence for amotivational syndrome. At worst, intoxication decreases a person's willingness to work on unappealing projects, but this effect hardly parallels the apathy typical of most definitions of amotivation. If these results qualify as evidence for amotivational

syndrome, then most psychoactive drugs could serve as a cause. In fact, anything that might create procrastination, including watching television, could serve as a source of amotivation.

Intoxication can impair performance on some tasks in some conditions. Nevertheless, the evidence lacks to prove clear amotivational syndrome. Many critics dismiss this laboratory evidence as irrelevant due reasons like short duration of exposure, yet that is not the case and there are other studies that demonstrate longer term exposure does not cause amotivation in animals.(630) The term often implies a failure to achieve in life, not simple deficits on laboratory tasks. To further test the role of cannabis in motivation, other investigators have examined marijuana's correlation with educational and work performance. Impairments on these life tasks appear more relevant to the idea of amotivational syndrome.

ii. Correlations with education and work do not support amotivational syndrome in cannabis users

Surveys of associations between drug use and job or school activities lack the experimental control found in the chronic administration studies. Investigators can only assume that cannabis use causes poor performance at work or school. Alternative explanations remain equally tenable. For example, poor adjustment in work or school might lead some people to use cannabis. A third factor may account for the association, too. Depressed people might perform poorly and choose to use cannabis. People with certain personality characteristics might choose to use marijuana and make school or work a low priority. Thus, a simple association between cannabis consumption and education or work does not prove that amotivational syndrome exists. Nevertheless, the absence of an association between cannabis and achievement might undermine arguments for cannabis-induced amotivation.

Parents and educators express understandable concern about marijuana, amotivational syndrome, and schoolwork. Research has focused on academic achievement in college and intoxicated school students. Contrary to popular belief, over half a dozen studies reveal that cannabis users and nonusers have comparable grades in college. One typical report surveyed 1,400 undergraduates, revealing no differences between users and nonusers on grades, changes in their majors, or number of colleges attended. Chronic users (those who used at least three times a week for three years) took more time off from their schooling, but were also more likely to plan to earn a graduate degree.(302)

Surprisingly, there is some evidence of improved academic performance in marijuana users than in nonusers, although no one has ever proposed that cannabis could help school performance.(239) Users and nonusers also show no differences in their orientations towards achievement, their extracurricular activities, or their participation in sports. Thus, research on college students provides no support for the idea of amotivational syndrome.(751)

Although cannabis consumption in college has no link to school performance, high school students who use cannabis have lower grades and quit school more often. Cannabis users in school also spend less time on their homework and miss more days of school.(347) At first glance, this association between cannabis and school performance seems consistent with the idea of amotivation. Perhaps cannabis destroys motivation in young teens, so an age restriction

would be appropriate. Yet, data do not support this restricted form of amotivational syndrome, either. Most heavy users earned lower grades prior to their cannabis consumption, suggesting that other factors besides cannabis might have caused the poorer performance.(621,622) For example, high school students who use cannabis heavily also tend to use alcohol and other illicit substances. These results suggest that drugs other than cannabis might lower grades.(276)

Cannabis alone probably does not cause poor school performance. Instead, the regular consumption of cannabis in school serves as part of a general pattern of deviance. Heavy users appear more unconventional in general. They are more critical of society, less involved in church and school, and more involved in delinquent acts. They often behaved this way before they ever discovered cannabis.(171) Because these young people showed these qualities before using cannabis, the drug seems an unlikely cause of amotivational syndrome in high school students. Thus, depressed, unmotivated, unconventional adolescents may choose to use marijuana, but the drug does not appear to create their deviance. Nonetheless, the DEA should apply age restrictions for the medical use of the cannabis.

Two contradictory attitudes have developed about marijuana's impact on job performance. Many people believe the drug destroys motivation and detracts from efficiency, yet others use the drug to enhance their work, which can be said in the case of many medical cannabis users who continue working while suffering a debilitating illness because cannabis helps.

The results seem to depend upon the type of job involved. People who perform repetitive, simple tasks may turn to cannabis to relieve from painful jobs. For example, laborers in India increased their ganja consumption 50 percent during the harvest season.(125) In Jamaica, farm hands who used cannabis actually worked harder than those who did not.(137,515) Perhaps marijuana makes monotonous physical labor more bearable. In contrast, jobs that require complex or rapid decisions likely suffer during intoxication.(119) Thus, the acute effects of cannabis on performance may vary dramatically with different jobs and the condition of the user.

The enduring lack of initiative that defines amotivational syndrome requires more than brief changes in work performance during intoxication. Wages, hours, and employment history may serve as better indices of motivation on the job. Research performed in countries where workers frequently use cannabis has shown little difference between heavy users, occasional users, and abstainers. These groups had comparable forms of employment in Costa Rica and Jamaica.(73,110)

In the United States, where cannabis consumption is less prevalent, the impact of the drug on wages, hours, and job turnover still does not support the idea of amotivational syndrome. Data actually suggest some positive links between cannabis consumption and work, but only for adults. One survey of over 8,000 adults who held a variety of jobs showed higher wages with increased use.(344) Other studies of employment histories and drug use reveal that marijuana users do not appear to lose their jobs more often than nonusers, even though employers are more likely to fire users of other illicit drugs.(494, 517)

iii. Summary for amotivational syndrome

Laboratory studies of humans and primates offer little support for amotivational syndrome for cannabis users. Employment data show no links between cannabis use and lower wages, poor work performance, or job turnover. School performance does not vary with cannabis consumption in college students. High school students who use cannabis do worse in school, but most performed poorly before they used cannabis, and many used other drugs that likely contributed to their lower grades more than cannabis. Nonetheless, appropriate age restrictions are necessary. Employment data show no links between cannabis use alone and lower wages, poor work performance, or job turnover in adults.

Self-reports in heavy users show that a percentage of people think cannabis affects their motivation, but consumption of other drugs or the presence of physical and emotional problems more likely are the cause of their lack of motivation. More importantly, these were not medical users who clearly indicate a beneficial therapeutic experience when using cannabis for severe medical conditions. Additionally, no studies show pervasive lethargy, dysphoria, and apathy appear in all heavy users. Thus, the evidence for a cannabis-induced amotivational syndrome is weak. Yet, a subset of depressed users may show the symptoms of amotivational syndrome.(185) These people would likely benefit from cognitive-behavioral treatments for depression, which can improve mood, motivation, and achievement.

B. Cannabis use has risks similar to other legal Schedule II substances

i. Overview

Amotivational syndrome is not the only social problem attributed to marijuana. The drug's potential role in auto accidents has also generated considerable concern. In 1997, traffic accidents in the U.S. numbered 16 million and caused 43,000 deaths. Comparable numbers of crashes and fatalities have likely occurred in more recent years.(84) These statistics raise an understandable concern about impaired driving. Many drugs can increase highway mishaps. Alcohol is the most common and notorious cause of accidents. Common antidepressants, antihistamines, and tranquilizers also reduce driving skill.(566)

Cannabis intoxication clearly alters thought and memory, leading many researchers to investigate its role in highway fatalities. Data supports that marijuana does not significantly contribute to accidents.(413, 669) Research on cannabis and traffic safety relies on two approaches: epidemiological studies of crashes and laboratory experiments with intoxicated drivers. In general, studies reveal that marijuana has no effect on culpability for fatal crashes if a driver's age and blood alcohol concentration are taken into account. There is no data regarding whether marijuana intoxication increases the chances of other more minor accidents. Regardless, driving while intoxicated is never acceptable and cannot be tolerated.

Laboratory experiments using driving simulators and actual performance on the road reveal that motorists intoxicated with cannabis compensate for the drug's cognitive effects. They drive more slowly, leave more space between cars, and take fewer risks. Nevertheless, dangerous situations might require rapid responses to avoid an accident, and recent work reveals

that the combination of alcohol and cannabis can meaningfully increase driving problems. Given marijuana's proven ability to impair attention and rapid responses, users must avoid driving while intoxicated.(485) Driving after consuming alcohol, particularly in combination with cannabis or any other drug, legal or illegal, even antihistamines, is extremely dangerous and ill-advised. These risks are similar to other Schedule II drugs.

ii. Epidemiological studies

Nearly a dozen studies from all around the globe report the frequent presence of THC in the bloodstreams of motorists involved in accidents that caused death or injury. It is important to note that depending on the study, as many as 84 percent of these users were intoxicated with alcohol at the time. Ethanol's detrimental effect on driving is well established, and seems the most parsimonious explanation for these mishaps.

For example, data from over 1,000 drivers involved in fatal accidents in Australia revealed that cannabis was present in 11 percent of them. Ratings of the accident reports revealed that drivers who had consumed alcohol or the combination of alcohol and cannabis were culpable more often than drivers who were free of drugs.(181).

Curiously, many studies of cannabis and traffic safety found that the odds of causing death or injury were slightly lower in cannabis users than in people who had not consumed drugs.(41) For example, the study of Australian motorists mentioned above showed that users of cannabis were 30 percent less likely to cause accidents as drivers who had not used any drug. A study of over 300 drivers involved in fatal crashes in California focused on motorists who tested positive for cannabis but no other drug. Unexpectedly, they were half as likely to be responsible for accidents as those who were free of substances.(730) Another investigation of over 1,800 fatal crashes in the U.S. found that drivers who used only cannabis were 70 percent as likely to have caused an accident as the drug-free group.(680)

Although, driving while intoxicated on any psychoactive substance is a problem, none of these estimates revealed statistically significant increases in causes of accidents as a result of using cannabis alone. Nevertheless, as the next section discusses, the consistency of these results raises interesting questions in which laboratory research provides a potential explanation.

iii. Laboratory experiments

Another approach to answering questions about cannabis and traffic safety involves randomly assigning motorists to ingest THC or placebo before driving. This approach has several advantages over epidemiological work. Critics might argue that epidemiological studies of THC's presence in crashes may create a confounding bias. They assert that people who choose to use marijuana and drive may be more disinhibited than those who do not drive during cannabis intoxication. Thus, any epidemiological evidence for elevated THC rates in drivers involved with accidents may simply reflect an underlying driving deficit correlated with the propensity to use cannabis before operating a motor vehicle.

Laboratory experiments can bypass this problem in two ways. First, researchers can randomly assign drivers to receive cannabis or placebo. This arrangement ensures that good and bad drivers are equally likely to end up in the group that uses marijuana before driving. Random

assignment assures that any identified deficits arise from intoxication rather than a biased sample. In an alternative approach, participants drive once after using a placebo and again after using cannabis. This technique, known as a within-subjects design, ensures that all the people drive both intoxicated and sober. Then, investigators can compare each individual's performance while intoxicated to his or her own performance in the absence of the drug. Again, under these circumstances, any identified impairment must stem from intoxication. Thus, laboratory experiments rule out alternative explanations for marijuana's impact on driving (and provide a safe laboratory environment for the test).

A review of over a dozen of these experiments reveals three findings. First, after using marijuana, people drive more slowly. In addition, they increase the distance between their cars and the car in front of them. Third, they are less likely to attempt to pass other vehicles on the road. All of these practices can decrease the chance of crashes and certainly limit the probability of injury or death if an accident does occur. These three habits may explain the slightly lower risk of accidents that appears in the epidemiological studies. These results contrast dramatically to those found for alcohol. Alcohol intoxication often increases speed and passing while decreasing following distance, and markedly raises the chance of crashes.(632)

Additional work has confirmed these effects.(555,556) One recent, comprehensive paper reported four different experiments examining the impact of THC and alcohol alone and in combination.(555) Men and women used cannabis containing zero, 100, 200, or 300 micrograms of THC per kilogram of body weight. The active doses correspond to approximately one-half, one, or one-and-a-half of a cannabis dose for a 150 pound person. Participants drank placebos or enough alcohol to maintain breath alcohol concentrations of approximately .04 percent (this dose corresponds approximately to drinking two beers quickly on an empty stomach for a 150 pound man). Participants then drove in different places on separate occasions, including a deserted stretch of road, in regular highway traffic, and on city streets. A driving instructor in a specially equipped training car, sat beside them, rating their performance (a second wheel and controls allowed the instructor to drive if needed). These studies have advantages over research that employs driving simulators because performance in a real car in regular traffic likely better generalizes to other driving situations.

In other tests, participants performed two different driving tasks. One task, the road-tracking test, simply involved maintaining a constant speed of 90 kilometers (roughly 55 miles) per hour and staying within a designated lane.(556) The other task, the car-following test, involved maintaining a constant distance behind a vehicle that altered its speed and acceleration. Marijuana produced two consistent effects. First, the drug significantly increased lateral movement within the traffic lane. That is, participants' cars weaved from side to side within the lane more after using cannabis than placebo. Second, cannabis caused drivers to increase their distance from the vehicle in front of them during the car-following test. Marijuana did not alter any other way that the drivers handled the vehicle, maneuvered through traffic, or turned the car. In contrast, alcohol not only increased lateral movement in the lane, it also impaired vehicle handling and maneuvers. The two drugs combined produced the most impairment.(556)

Thus, although traffic accidents kill thousands each year and driving while intoxicated with cannabis is not tolerable, its role alone in reckless driving is markedly smaller than once

believed. Epidemiological research reveals that those who test positive for cannabis and no other drug do not cause accidents any more often than people who are drug free. Laboratory research shows that cannabis intoxication increases lateral motion within the traffic lane but does not impair handling, maneuvering, or turning. Obviously, no one should operate dangerous machinery of any kind under the influence of cannabis or other psychoactive drugs. Nevertheless, the impact of cannabis alone on reckless driving appears extremely small. Although traffic fatalities remain a serious social problem, cannabis use alone does not appear to be a significant causative factor.

C. Cannabis use does not increase aggression

i. Overview

In addition to concerns about loss of motivation and reckless driving, many people fear that cannabis intoxication can lead to hostility. Summaries of studies on marijuana and aggression may reveal these biases more than any other area of research. Interpretations of this literature are incredibly disparate. One author's evidence for marijuana's connection to violence serves as another author's proof that the drug does not cause aggression.

An interpretation of a study of murderers illustrates this point. In this research, interviews with 268 incarcerated murderers revealed that 72 of them had used cannabis within a day of the homicide. Of these 72, 18 claimed that marijuana contributed to the murder in some way. Fifteen of these 18 were intoxicated with other drugs at the time.(643) The researchers reported these facts clearly, but interpretations of their meaning vary dramatically. One review cites this study as an example of cannabis leading to violence.(667) Another uses it as an illustration of the rarity of cannabis-induced hostility, emphasizing how other drugs account for the relationship between cannabis and aggression.(751) Thus, any interpretations of data from this field require a close reading of the original studies.

People have assumed drugs lead to violence at least since the seventeenth century, and certainly intoxication, withdrawal, and chronic use of alcohol and stimulants clearly increase aggressive acts.(358) Despite evidence for increased aggression that is otherwise associated with other drugs, the vast majority of work shows that cannabis does not induce hostility. This research includes the standard series of case studies, correlational reports, and laboratory experiments.

Each of these research approaches has strengths and weaknesses, but the general conclusions remain the same: direct links between cannabis intoxication and violence do not appear in the general population. A few studies show correlations between marijuana consumption and violent acts, but these links frequently stem from personality characteristics or the use of other drugs. People who are violent or who use drugs that lead to violence often also use cannabis, but it is not clear that the cannabis use causes the violence.

Laboratory studies also find no link between THC intoxication and violence. Most people who ingest THC before performing a competitive task in the laboratory do not show more aggression than people who receive placebos; occasionally they show decreased hostility. Numerous scientific panels sponsored by various governments invariably report that marijuana does not lead to violence.(751)

ii. Historical precedent

Cannabis use dates back more than a thousand years. There have been many differing reports about cannabis throughout history, some supportive of its medical use, and some reports have focused on its negative, or in most cases, perceived negative side-effects.(114) Harry Anslinger, the first head of the Federal Bureau of Narcotics, cited the negative history as evidence of marijuana-induced aggression.(69) Modern authors still suggest that the drug leads to hostility.(613) It is clear that this misunderstanding stems from biases and poor interpretations of history and individual case studies.

Some of the most sensationalistic case studies came from the Bureau of Narcotics in the 1930s that told of users who committed heinous crimes. Many times the details did not reveal if the crime actually occurred during marijuana intoxication or some other issue. Yet, some focused on marijuana's link to violence. A classic example concerned a Florida murder case from 1933. Initial newspaper reports attributed the murders to the drug, and Harry Anslinger used the case as an example for many years. Despite these reports of this event, further investigation revealed that the murderer suffered from a serious psychotic, mental illness, and many members of his family also struggled with psychotic disorders. He may have had a history of violence prior to his drug use, yet none of these possibilities appeared in press.(350) A close look at another case study that the Bureau of Narcotics frequently cited revealed that the criminal had claimed to use marijuana when, in fact, he had not.(80)

iii. Crime

A more scientific way to investigate marijuana's alleged link to violence appeared in studies of crime rates. Researchers have looked for an association between violent crime and cannabis consumption for at least 70 years. This association does not prove that marijuana causes aggression, but any theory linking cannabis and violence would suggest that the two should covary. Early studies of military personnel, arrestees, and patients in mental hospitals revealed no relationship between cannabis and violent crime.

One typical study examined rates of aggressive crime in military prisoners. Marijuana users were no more likely to commit crimes of violence than nonusers.(79) Some studies revealed fewer antisocial behaviors in cannabis users than in users of other drugs.(2) Later research confirmed these findings. For example, a study of 109 delinquent juveniles revealed that violent offenses had no link with cannabis consumption, but significant associations with cocaine and amphetamine use.(627)

A few recent studies reported small but statistically significant associations between marijuana consumption and violence in select groups of adolescents. Yet, the effects were extremely small, meaning that the amount of violence increased only a little as the amount of cannabis consumption increased a lot. (Correlations were approximately .20 and only reached statistical significance because of the large sample sizes). These studies asked teens about their marijuana use as well as the frequency of their aggressive acts, but failed to assess if they were intoxicated when they were hostile. Thus, they alone do not support the idea that cannabis causes violence. Instead, a subset of teens may choose both to use marijuana and behave aggressively because of an underlying personality characteristic or tendency.(1, 665, 725, 726) People who have trouble inhibiting themselves might engage in both cannabis consumption and

violent behavior, yet neither one caused the other. The use of other drugs, including alcohol, may be a more likely explanation for the aggression. In fact, when one group of researchers included previous violence and alcohol consumption in their analyses, the links between marijuana and aggression disappeared.(725)

Other studies suggest that these small links between cannabis consumption and hostility do not mean that marijuana intoxication leads to aggression. For example, a group of adolescents charged with violent crimes reported that cannabis was likely to decrease aggressiveness.(685) Less than four percent of people report that they think marijuana makes them angry or hostile.(272, 608) Research participants have lower scores on questionnaires designed to assess hostility, anger, and aggressiveness if they answer after using cannabis.(2) Yet, some of the most compelling evidence that the drug does not increase hostility stems from laboratory work that actually measures belligerent behavior.

iv. Laboratory research

A sophisticated way to examine marijuana's impact on aggression requires providing THC to participants in the laboratory. Few people behave in a hostile fashion in a formal setting, so most studies provoke participants to see if they will aggress in response. A popular paradigm uses a competitive game. The participant competes against an opponent to provide a faster, correct response. The winner of each trial can give the loser a mild electric shock. (A later version of the task allows the winner to take money or points from the loser). In fact, the opponent is bogus and the results are fixed. The participant loses a specified number of times. The experimenter makes it seem as if the opponent provides increasing or heavy penalties in an effort to provoke aggression. This paradigm may seem an absurd analogue to hostile interactions in everyday life, yet former prisoners with histories of aggressive acts do behave more aggressively in this game. Frustration, drug withdrawal, and other conditions that should increase violence also increase aggression in the game.(124) Laboratory studies using this paradigm find that marijuana intoxication rarely heightens hostile responses. Participants gave stronger shocks when intoxicated with alcohol, but THC had no impact. A high dose of THC actually lowered aggression, despite the provocation inherent in the task.(472, 679) These results suggest that cannabis intoxication does not increase aggression in a normal population.

v. Conclusion: cannabis alone does not cause aggression

Cannabis intoxication does not lead to aggression in the general population. Self-reports of experienced users suggest that the drug makes them feel calm rather than hostile and unfriendly. History and research on crime reveals little impact of cannabis on violence. The vast majority of laboratory research shows that cannabis intoxication does not increase hostility and action. Associations between cannabis and aggression arise in small subsets of the population, usually involving individuals experiencing other unrelated co-occurring conditions. The drug's general absence of an impact on hostility has led every major commission report to conclude that cannabis does not increase aggression.

D. Conclusions on public health factor

Some have concerns that cannabis creates meaningful social problems, including amotivational syndrome, reckless driving, and aggression. However, research in each of these domains reveals that these concerns are unfounded. Evidence for a cannabis-induced amotivational syndrome is lacking. A subset of depressed users may have inspired a few case studies that report apathy, indifference, and dysphoria, but cannabis likely does not cause these symptoms. The drug does not correlate with low grades in college students. High school students who use marijuana have lower grades, but their poor school performance occurred prior to their consumption of cannabis. Cannabis users do not show worse performance on the job, more frequent unemployment, or lower wages. In addition, long-term exposure to cannabis in the laboratory fails to show any meaningful or consistent impact on productivity.

Clearly, no one should drive while intoxicated. Yet links between cannabis use and reckless driving are weak, and usually stem from co-occurring alcohol consumption. People with THC but no alcohol in their blood do not have higher rates of culpability for traffic accidents than drug-free drivers. Laboratory experiments that administer THC and placebo to motorists reveal an increased weaving within the lane that accompanies intoxication. Yet, these drivers also spontaneously slow their speed, increase their following distance, and rarely attempt to pass other cars. In contrast, alcohol, even at relatively low doses, clearly impairs driving.

The association between cannabis intoxication and aggression is also unlikely. Most studies of violent crime show no link to marijuana use or small correlations that suggest a few aggressive people also happen to use cannabis. Laboratory research on general samples shows no increases in aggression during intoxication. Concerns about productivity, impaired driving, and hostility are certainly important, but restricting marijuana consumption seems to have little impact on these social problems.

CONCLUSION AND POSSIBLE FUTURE DIRECTIONS

The United States Justice Department remains committed to the enforcement of the Controlled Substances Act. Because the department "is also committed to making efficient and rational use of its limited investigative and prosecutorial resources," and must appropriately reclassify drug substances when medical and scientific evidence requires as presented in this report, the DEA after the FDA scientific review, following the eight-factor analysis and evidence presented here, should reclassify cannabis as a Schedule II substance.(682)

The Obama administration has acknowledged the "compassionate use" that some states' electorates have provided for. While cannabis is not a benign drug, mounting scientific evidence and consensus of medical opinion support rescheduling to Schedule II, the most highly regulated schedule.

Some very ill people have had very difficult times finding safe and reliable sources, and some have had to fight long court battles to defend themselves for the use of a compound that irrefutably works to help relieve painful symptoms from serious illnesses like treatment for HIV/AIDS wasting syndrome, amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, and multiple sclerosis (MS).

On multiple occasions the DEA has studied the medicinal properties of cannabis. A DEA Administrative Law Judge concluded that, "the evidence clearly shows that marijuana is capable of relieving the distress of great numbers of very ill people, and doing so with safety under medical supervision…it would be unreasonable, arbitrary and capricious for the DEA to continue to stand between those sufferers and the benefits of this substance."(40) However, the DEA overruled the opinion, and then denied two subsequent petitions despite the mounting scientific evidence. Since the last FDA review in 2006, the scientific process has identified and clarified even more of the therapeutic effects of cannabis through ongoing research and assessment of available data. This petition presents this further evidence. It is now time for the DEA to reschedule the substance.

There are other possible futures and ways to make the medicinal use of cannabis viable for patients in need while addressing public health issues. Concerns are often raised about lack of quality control in using medicinal cannabis, including lack of dosing paradigms, safe methods of use, and inability to safely access cannabis. One possible future would be to allow for the legal, regulated growth of cannabis for medicinal use. It is now a relatively easy and affordable task to use DNA analysis via polymerase chain reaction (PCR) and gel electrophoresis testing to provide an extremely accurate characterization of a plant's genetic make-up. Accurate analytical kits are available that would make this accessible to even small scale farmers. These techniques would also foster the creation of unique genetic hybrids grown specifically to maximize therapeutic medicinal potential.

At the pharmacy level it is now possible to easily and inexpensively perform quantitative analysis to identify the levels of cannabinoids, including chemical and physical properties, such as chemical reactivity, solubility, molecular weight, melting point, etc. via techniques such as gas

chromatography-mass spectrometry (GC-MS), mass selective detectors (MSD), operating in either electron ionization (EI) or negative-ion chemical ionization (NICI) mode. These methods are fully validated, and the validated parameters included linearity, selectivity, accuracy, precision, and extraction efficiency. Thus cannabis plants could be grown under controlled settings, with harvesting of the flowers, which after proper drying, would be quantitatively evaluated for specific cannabinoid levels.

These dried, cured flowers would then go to a compounding pharmacist. Pharmaceutical compounding is a longstanding traditional role for pharmacists. It is a process by which a pharmacist combines ingredients into a customized medication for an individual patient. Compounding is now increasingly offered by community pharmacies as a specialized service. Studies have shown that pharmacists providing compounding reported that this has increased the quality of pharmaceuticals and improves collaboration between the patient, physician, and pharmacist, while empowering the patient and improving professional satisfaction of the physician and pharmacist.(422) This would allow safe access to a medicine with proven efficacy and acceptable safety, in a manner that does not endanger the patient and allows for reasonable regulatory oversight.

The evidence presented in this report proves the addiction, dependence, abuse and misuse potential are all low compared with other Schedule II drugs. Like other controlled substances in schedule II or III, the public health concerns remain, but none that outweigh the fact that cannabis is a medically acceptable drug for patients with serious conditions. Cannabis does not present a potential for abuse to justify remaining a Schedule I substance. It remains that no one should drive a vehicle intoxicated, and children should not use cannabis – both statements are true for almost all other Schedule II substances. There are well researched accepted medical uses; there are ways to safely administer the drug; and, there are effective non-smoking methods like vaporization, oral ingestion or topical application. The DEA and FDA should use this rule-making process to clarify appropriate use standards, including age restrictions.

The National Academy of Sciences, Institute of Medicine perhaps sums it up best (715): “Marijuana is not, to be sure, a completely benign substance. It is a powerful drug that affects the body and mind in a variety of ways. However, except for the damage caused by smoking [*which this petition clearly describes non-smoking methods for medical use*], its adverse effects resemble those of many approved medications.” [Italics added]

Current federal rules preclude the adoption of reasonable and workable frameworks for providing access to patients while maintaining the ability of law enforcement agencies to address non-medical/illegal distribution and use of cannabis. The situation has become untenable. The solution lies with the federal government. The DEA should initiate rulemaking proceedings to reclassify medical cannabis as a Schedule II drug so qualifying patients who follow law may obtain the medication they need through the traditional and safe method of physician prescribing and pharmacy dispensing.

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