JAN 17 2001

Mr. Donnie R. Marshall
Administrator
Drug Enforcement Administration
Washington, D.C. 20537

Dear Mr. Marshall:

In response to your request dated December 17, 1997, and pursuant to the Controlled
Substances Act (CSA), 21 U.S.C. § 811 (b), (c), and (f), the Department of Health and
Human Services (DHHS) recommends that marijuana
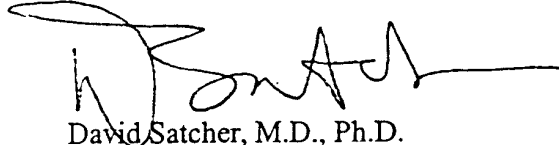continue to be subject to control under Schedule I.

Marijuana and the tetrahydrocannabinols are currently controlled under Schedule I of the
CSA. Marijuana continues to meet the three criteria for placing a substance in Schedule I
of the CSA under 21 U.S.C. 812(b)(1). As discussed in the attached analysis, marijuana
has a high potential for abuse, has no currently accepted medical use in treatment in the
United States, and has a lack of accepted safety for use under medical supervision.
Accordingly, HHS recommends that marijuana   continue to
be subject to control under Schedule I of the CSA.

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You will find enclosed two documents prepared by FDA's Controlled Substance Staff that are the bases for the recommendations.

Should you have any questions regarding these recommendations, please contact Corinne P. Moody, Science Policy Analyst, Controlled Substance Staff at (301) 827-1999.

Sincerely yours,

David Satcher, M.D., Ph.D.
Assistant Secretary for Health
and Surgeon General

Enclosures

BASIS FOR THE RECOMMENDATION FOR MAINTAINING MARIJUANA IN SCHEDULE I OF THE CONTROLLED SUBSTANCES ACT

A.   BACKGROUND

On July 10, 1995, Mr. Jon Gettman submitted a petition to the Drug Enforcement Administration (DEA) requesting that proceedings be initiated to repeal the rules and regulations that place marijuana and the tetrahydrocannabinols in Schedule I of the Controlled Substances Act (CSA) and dronabinol and nabilone in Schedule II of the CSA. The petition contends that evidence of abuse potential is insufficient for each substance or class of substances to be controlled in Schedule I or II of the CSA. In December 1997, the DEA Administrator requested that the Department of Health and Human Services (DHHS) develop scientific and medical evaluations and recommendations as to the proper scheduling of the substances at issue, pursuant to 21 U.S.C. 811(b).

This document responds to the portion of the petition that concerns marijuana

In accordance with 21 U.S.C. 811(b), the DEA has gathered information, and the Secretary of DHHS has considered eight factors in a scientific and medical evaluation, to determine how to schedule and control marijuana (*Cannabis sativa*) under the CSA. The eight factors are: actual or relative potential for abuse, scientific evidence of pharmacological effects, scientific knowledge about the drug or substance in general, history and current patterns of abuse, the scope and duration and significance of abuse, the risk (if any) to public health, psychic or physiologic dependence liability, and whether the substance is an immediate precursor of a substance that is already controlled. If appropriate, the Secretary must also make three findings - related to a substance's abuse potential, legitimate medical use, and safety or dependence liability - and then a recommendation. This evaluation presents scientific and medical knowledge under the eight factors, findings in the three required areas, and a recommendation.

Administrative responsibilities for evaluating a substance for control under the CSA are performed by the Food and Drug Administration (FDA), with the concurrence of the National Institute on Drug Abuse (NIDA), as described in the Memorandum of Understanding (MOU) of March 8, 1985 (50 FR 9518-20).

Pursuant to 21 U.S.C. 811(c), the eight factors pertaining to the scheduling of marijuana are considered below. The weight of the scientific and medical evidence considered under these factors supports the three findings that: (1) marijuana has a high potential for abuse, (2) marijuana has no currently accepted medical use in treatment in the United States, and (3) there is a lack of accepted evidence about the safety of using marijuana under medical supervision.

B.   EVALUATING MARIJUANA UNDER THE EIGHT FACTORS

This section presents scientific and medical knowledge about marijuana under the eight required factors.

1.   ITS ACTUAL OR RELATIVE POTENTIAL FOR ABUSE

The CSA defines marijuana as the following:

> all parts of the plant Cannabis Sativa L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin. Such term does not include the mature stalks of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination.

21 U.S.C. § 802(16).

The term "abuse" is not defined in the CSA. However, the legislative history of the CSA suggests the following in determining whether a particular drug or substance has a potential for abuse:

b.　　Individuals are taking the substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.

c.　　There is a significant diversion of the drug or substance from legitimate drug channels.

d.　　Individuals are taking the substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such substances.

e.　　The substance is so related in its action to a substance already listed as having a potential for abuse to make it likely that it will have the same potential for abuse as such substance, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.

Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970) reprinted in U.S.C.C.A.N. 4566, 4603.

In considering these concepts in a variety of scheduling analyses over the last three decades, the Secretary has analyzed a range of factors when assessing the abuse liability of a substance. These factors have included the prevalence and frequency of use in the general public and in specific sub-populations, the amount of the material that is available for illicit use, the ease with which the substance may be obtained or manufactured, the reputation or status of the substance "on the street", as well as evidence relevant to population groups that may be at particular risk.

Abuse liability is a complex determination with many dimensions. There is no single test or assessment procedure that, by itself, provides a full and complete characterization. Thus, no single measure of abuse liability is ideal. Scientifically, a comprehensive evaluation of the relative abuse potential of a drug substance can include consideration of the drug's receptor binding affinity, preclinical pharmacology, reinforcing effects, discriminative stimulus effects, dependence producing potential, pharmacokinetics and route of administration, toxicity, assessment of the clinical efficacy-safety database relative to actual abuse, clinical abuse liability studies and the public health risks following introduction of the substance to the general population. It is important to note that abuse may exist independent of a state of physical dependence, because drugs may be abused in doses or in patterns that do not induce physical dependence.

Animal data and epidemiological data are both used in determining a substance's abuse liability. While animal data may help the Secretary draw conclusions on the abuse liability of a substance, data regarding human abuse, if available, is given greater weight. For example, even if a

compound fails to display abuse liability in animal laboratory testing, positive evidence of abuse liability in humans is given greater weight. Epidemiological data can also be an important indicator of actual abuse and may, in some circumstances, be given greater weight than laboratory data. Thus, in situations where the epidemiological data indicates that a substance is abused, despite the lack of positive abuse liability indications in animal or human laboratory testing, the abuse liability determination may rest more heavily on the epidemiological data. Finally, evidence of clandestine production and illicit trafficking of a substance are also important factors to consider as this evidence sheds light on both the demand for a substance as well as the ease with which it can be obtained.

The Secretary disagrees with Mr. Gettman's assertion that "[t]he accepted contemporary legal convention for evaluating the abuse potential of a drug or substance is the relative degree of self-administration the drug induces in animal subjects." As discussed above, self-administration tests that identify whether a substance is reinforcing in animals are but one component of the scientific assessment of the abuse potential of a substance. Positive indicators of human abuse liability for a particular substance, whether from laboratory studies or epidemiological data, are given greater weight than animal studies suggesting the same compound has no abuse potential.

Throughout his petition, Mr. Gettman argues that while many people "use" marijuana, few "abuse" it. He appears to equate abuse with the level of physical dependence and toxicity resulting from marijuana use. Thus, he appears to be arguing that a substance that causes only low levels of physical dependence and toxicity must be considered to have a low potential for abuse. The Secretary does not agree with this argument. Physical dependence and toxicity are not the only factors that are considered in determining a substance's abuse potential. The actual use and frequency of use of a substance, especially when that use may result in harmful consequences such as failure to fulfill major obligations at work or school, physical risk-taking, or even substance-related legal problems, are indicative of a substance's abuse potential.

a.   **There is evidence that individuals are taking the substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.**

Marijuana is a widely used substance. The pharmacology of the psychoactive constituents of marijuana (including delta^9-THC, the primary psychoactive ingredient in marijuana) has been studied extensively in animals and humans and is discussed in more detail below in Section 2, "Scientific Evidence of its Pharmacological Effects, if Known." Although it is difficult to determine the full extent of marijuana abuse, extensive data from the National Institute on Drug Abuse (NIDA) and from the Substance Abuse Mental Health Services Administration (SAMHSA) are available. These data are discussed in detail in Section 4 "Its History and Current Pattern of Abuse;" Section 5, "The Scope, Duration, and Significance of Abuse;" and Section 6, "What, if any Risk There is to the Public Health."

According to the National Household Survey on Drug Abuse (NHSDA), of the 14.8 million Americans who used illicit drugs on a monthly basis in 1999, 11.2 million used marijuana. In 1998, 1.6 million children between the ages of 12 and 17 used marijuana for the first time. (See the discussion of the 1999 NHSDA in Section 4). A 1999 survey of 8th, 10th, and 12th grade

students indicates that marijuana is the most widely used illicit drug in this age group. By 12th grade, 37.8% of students report having used marijuana in the past year, and 23.1 % report using it monthly. (See the discussion of the Monitoring the Future Study in Section 4). Primary marijuana abuse accounts for 13% of the admissions to treatment facilities for substance abuse, with 92% of those admitted having used marijuana for the first time by age 18. (See discussion of the Treatment Episode Data Set in Section 4).

The Drug Abuse Warning Network (DAWN) is a national probability survey of hospitals with emergency departments (EDs). DAWN is designed to obtain information on ED episodes that are induced by or related to the use of an illegal drug or the non-medical use of a legal drug. DAWN recently reported 87,150 ED drug mentions for marijuana/ hashish in 1999, representing 16 % of all drug-related episodes in 1999. (See discussion of DAWN in Section 4). In 1999, DAWN data show that out of 664 medical examiner marijuana-related episodes, there were 187 deaths in persons who had used marijuana alone. While marijuana has a low level of toxicity when compared to other drugs of abuse, there are a number of risks resulting from both acute and chronic use of marijuana. These risks are discussed in full in sections 2 and 6 below.

b.   There is significant diversion of the substance from legitimate drug channels.

Because cannabis is currently available through legitimate channels for research purposes only, there is limited legitimate use of this substance and thus limited potential for diversion. The lack of significant diversion of investigational supplies may also result from the ready availability of cannabis of equal or greater potency through illicit channels.

The magnitude of the demand for marijuana is, however, evidenced by the Drug Enforcement Administration (DEA) / Office of National Drug Control Policy (ONDCP) statistics. Data on marijuana seizures can often highlight trends in the overall trafficking patterns. The DEA's Federal-Wide Drug Seizure System (FDSS) provides information on total federal drug seizures. FDSS reports total federal seizures of 699 metric tons of marijuana in fiscal year 1997, 825 metric tons in fiscal year 1998 and 1,175 metric tons in fiscal year 1999 (ONDCP, 2000).

c.   Individuals are taking the substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such substances.

The 1998 NHSDA suggests that 6.8 million individuals use marijuana on a weekly basis (SAMHSA, 1998), confirming that marijuana has reinforcing properties for many individuals. The FDA has not approved a new drug application for marijuana, although research under several INDs is currently active. Based on the large number of individuals who use marijuana, it can be concluded that the majority of individuals using cannabis do so on their own initiative, not on the basis of medical advice from a practitioner licensed to administer the drug in the course of professional practice.

d.   The substance is so related in its action to a substance already listed as having a potential for abuse to make it likely that it will have the same potential for abuse as such substance, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical

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advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.

Two drug products that contain cannabinoid compounds that are structurally related to the active components in marijuana are already regulated under the CSA. These are Marinol (dronabinol, delta^9-THC), which is a Schedule III drug, and nabilone, which is a Schedule II drug. All other cannabinoid compounds that are structurally related to the active components in marijuana are listed as Schedule I drugs under the CSA. Cannabinoid compounds constitute a distinct pharmacological class that is unrelated to other drugs currently listed in the CSA. The primary psychoactive compound in botanical marijuana is delta^9-tetrahydrocannabinol (delta^9-THC). Other cannabinoids also present in the marijuana plant likely contribute to the psychoactive effects. Individuals administer the constituents of marijuana by burning the material and inhaling (smoking) many of its combustible and vaporized products. The route of administration of a drug is one component of its abuse potential. Most psychoactive drugs exert their maximum subjective effects when blood levels of the drug are rapidly increased. Inhalation of drugs permits a rapid delivery and distribution of the drug to the brain. The intense psychoactive drug effect, which can be rapidly achieved by smoking, is often called a "rush" and generally is considered to be the effect desired by the abuser. This effect explains why marijuana abusers prefer the inhalation, intravenous or intranasal routes rather than oral routes of administration. Such is also the case with cocaine, opium, heroin, phencyclidine, and methamphetamine (Wesson & Washburn, 1990).

2. SCIENTIFIC EVIDENCE OF ITS PHARMACOLOGICAL EFFECTS, IF KNOWN

We concur with the petitioner that there is abundant scientific data available on the neurochemistry, toxicology, and pharmacology of marijuana. This section includes a scientific evaluation of marijuana's neurochemistry and pharmacology, central nervous system effects including human and animal behavior, pharmacodynamics of central nervous system effects, cognitive effects, cardiovascular and autonomic effects, endocrine system effects and immunological system effects. The overview presented below relies upon the most current research literature on cannabinoids.

NEUROCHEMISTRY AND PHARMACOLOGY OF MARIJUANA

To date, a total of 483 natural constituents have been identified in marijuana of which approximately 66 belong to the general group known as cannabinoids (Ross and ElSohly, 1995). The cannabinoids appear to be unique to marijuana, and most of those occurring naturally have already been identified. Within the cannabinoids, delta-9-tetrahydrocannabinol (delta^9-THC) is considered the major psychoactive constituent of marijuana. Since the elucidation of the structure and discovery of the function of delta^9-THC, in 1964 by Gaoni and Mechoulam, cannabis and cannabinoid research has flourished. Substantial discoveries on the pharmacology, biochemistry and behavioral mechanisms of action of the cannabinoids have been accomplished, and laid the scientific foundations for a better understanding of the effects of marijuana.

There is conclusive evidence of the existence of at least two cannabinoid receptors, CB_1 and CB_2, and it is now known that some of the pharmacological effects of cannabinoids are mediated

through activation of these receptors. The cannabinoid receptors belong to the G-protein-coupled receptors family and present a typical seven transmembrane-spanning domain structure. Many G-protein coupled receptors are linked to adenylate cyclase, and stimulation of these receptors might result, either in inhibition or activation of adenylate cyclase, depending on the receptor system. Cannabinoid receptors are linked to an inhibitory G protein (Gi), meaning that when activated, inhibition of the activity of adenylate cyclase occurs, thus preventing the conversion of ATP to the second messenger cyclic AMP (cAMP). Examples of inhibitory-coupled receptors include opioid, muscarinic, α_2-adrenoreceptors, dopamine (D_2) and serotonin (5-HT_1) among others. The pharmacological relevance of the adenylate cyclase inhibition has been difficult to determine (Adams and Martin, 1996).

Advances in molecular biology allowed the cloning of a cannabinoid receptor (Matsuda *et al.*, 1990), first from rat brain origin followed by the cloning of the human receptor (Gerard *et al.*, 1991) therefore offering definitive evidence for a specific cannabinoid receptor. Autoradiographic studies have provided information on the distribution of cannabinoid receptors. CB_1 receptors are present in the brain and spinal cord and in certain peripheral tissues. The distribution pattern of these receptors within the central nervous system is heterogeneous. It is believed that the localization of these receptors in various regions of the brain, such as basal ganglia, cerebellum, hippocampus and cerebral cortex, may explain cannabinoid interference with movement coordination and effects on memory and cognition. Concentration of CB_1 receptors is considerably lower in peripheral tissues than in the central nervous system (Henkerham *et al.*, 1990 and 1992). CB_2 receptors have been detected only outside the central nervous system. Their occurrence has been shown to be primarily in immune tissues such as leukocytes, spleen and tonsils and it is believed that the CB_2-type receptor is responsible for mediating the immunological effects of cannabinoids (Galiegui *et al.*, 1995).

Recently it has been shown that CB_1 but not CB_2 receptors inhibit N- and Q type calcium channels and activate inwardly rectifying potassium channels. Inhibition of the N-type calcium channels decreases neurotransmitter release from several tissues and this may the mechanism by which cannabinoids inhibit acetylcholine, noradrenaline and glutamate release from specific areas of the brain. These effects might represent a potential cellular mechanism underlying the antinociceptive and psychoactive effects of cannabinoids (Ameri, 1999).

Several synthetic cannabinoid agonists have been synthesized and characterized and selective antagonists for both receptors have been identified. In 1994, SR-141716A, the first selective antagonist with CB_1 selectivity was identified, and more recently the selective CB_2 receptor antagonist, SR-144528, was described (Rinaldi-Carmona *et al.*, 1994 and 1998). In general, antagonists have proven to be invaluable tools in pharmacology. They allow the identification of key physiological functions by the receptors, through the blockade of their responses.

Delta⁹-THC displays similar affinity for CB_1 and CB_2 receptors but behaves as a weak agonist for CB_2 receptors as judged by inhibition of adenylate cyclase. The identification of synthetic cannabinoid ligands deprived of the typical THC-like psychoactive properties, that selectively bind to CB_2 receptors, supports the idea that the psychotropic effects of cannabinoids are mediated through the activation of CB_1-receptors (Hanus *et al.*, 1999). Furthermore, cannabinoid agonists such as delta⁹-THC and the synthetic ones, WIN-55,212-2 and CP-55,940, produce

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hypothermia, analgesia, hypoactivity and cataplexy. These effects are reversed by the selective CB$_1$ antagonist, SR-141716A, providing good evidence for the involvement of a CB$_1$ receptor mediated mechanism.

In addition, the discovery of the endogenous cannabinoid receptor agonists, anandamide and arachidonyl glycine (2-AG) confirmed the belief of a central cannabinoid neuromodulatory system. Indeed, cannabinoid and their endogenous ligands are present in central as well as peripheral tissues. Mechanisms for the synthesis and metabolism of anandamide have been described. The physiological roles of endogenous cannabinoids are not yet fully characterized, although it has been the target of large research efforts (Martin et al., 1999).

In conclusion, progress in cannabinoid pharmacology, including the characterization of the cannabinoid receptors, isolation of endogenous cannabinoid ligands, synthesis of agonists and antagonists with diverse degree of affinity and selectivity for cannabinoid receptors, have provided the foundation for the elucidation of the specific effects mediated by cannabinoids and their roles in psychomotor disorders, memory, cognitive functions, analgesia, antiemesis, intraocular and systemic blood pressure modulation, broncodilation, and inflammation.

The reinforcing properties of a number of commonly abused drugs such as amphetamine, cocaine, alcohol, morphine and nicotine, have been explained by the effects of these drugs in the activation of dopaminergic pathways in certain areas of the brain and in particular the mesolimbic dopaminergic system (Koob, 1992). It has been demonstrated that delta^9-THC increases dopamine activity in reward relevant circuits in the brain (French, 1997; Gessa, et al. 1998), but the mechanism of these effects and the relevance of these findings in the context of the abuse potential of marijuana is still unknown.

CENTRAL NERVOUS SYSTEM EFFECTS

HUMAN BEHAVIORAL EFFECTS

As with other psychoactive drugs, the response that an individual has to marijuana is dependent on the set (psychological and emotional orientation) and setting (circumstances) under which the individual takes the drug. Thus, if an individual uses marijuana while in a happy state of mind among good friends, the responses are likely to be interpreted as more positive than if that individual uses the drug during a crisis while alone.

The mental and behavioral effects of marijuana can vary widely among individuals, but common responses, described by Wills (1998) and others (Adams and Martin 1996; Hollister 1986a, 1988a; Institute of Medicine 1982) are listed below:

1) Dizziness, nausea, tachycardia, facial flushing, dry mouth and tremor can occur initially
2) Merriment, happiness and even exhilaration at high doses
3) Disinhibition, relaxation, increased sociability, and talkativeness
4) Enhanced sensory perception, giving rise to increased appreciation of music, art and touch
5) Heightened imagination leading to a subjective sense of increased creativity
6) Time distortions

7) Illusions, delusions and hallucinations are rare except at high doses
8) Impaired judgement, reduced co-ordination and ataxia, which can impede driving ability or lead to an increase in risk-taking behavior
9) Emotional lability, incongruity of affect, dysphoria, disorganized thinking, inability to converse logically, agitation, paranoia, confusion, restlessness, anxiety, drowsiness and panic attacks may occur, especially in inexperienced users or in those who have taken a large dose
10) Increased appetite and short-term memory impairment are common

Humans demonstrate a preference for higher doses of marijuana (1.95% delta^9-THC) over lower doses (0.63% delta^9-THC) (Chait and Burke, 1994), similar to the dose preference exhibited for many other drugs of abuse.

ANIMAL BEHAVIORAL EFFECTS

• Predictors of Reinforcing Effects (Self-Administration and Conditioned Place Preference)_

One indicator of whether a drug will be reinforcing in humans is the self-administration test in animals. Self-administration of marijuana, LSD, sigma receptor agonists, or cholinergic antagonists is difficult to demonstrate in animals. However, when it is known that humans voluntarily consume a particular drug for its pleasurable effects, the inability to establish self-administration with that drug in animals has no practical importance. This is because the animal test is only useful as a rough predictor of human behavioral response in the absence of naturalistic data. Thus, the petitioner is incorrect that the accepted legal convention for abuse potential is self-administration in animals and that because marijuana does not induce self-administration in animals, it has a lower abuse potential than drugs that easily induce self-administration in animals. Similarly, the petitioner is incorrect that the difficulty in inducing self-administration of marijuana in animals is due to a lack of effect on dopamine receptors. In fact, dopamine release can be stimulated indirectly by marijuana, following direct action of the drug on cannabinoid receptors. However, it is important to note that while self-administration in animals has been correlated with dopamine function, both pleasurable and painful stimuli can evoke dopaminergic responses. Dopamine functioning does not determine scheduling under the CSA.

Naïve animals will not typically self-administer cannabinoids when they must choose between saline and a cannabinoid. However, a recent report shows that when squirrel monkeys are first trained to self-administer intravenous cocaine, they will continue to bar-press at the same rate when THC is substituted for cocaine, at doses that are comparable to those used by humans who smoke marijuana (Tanda *et al.*, 2000). This effect was blocked by the cannabinoid receptor antagonist, SR 141716. These data demonstrate that under specific pretreatment conditions, an animal model of reinforcement by cannabinoids now exists for future investigations. Additionally, mice have been reported to self-administer WIN 55212, a CB$_1$ receptor agonist with a non-cannabinoid structure (Martellotta *et al.*, 1998). There may be a critical dose-dependent effect, though, since aversive effects, rather than reinforcing effects, have been described in rats with high doses of WIN 55212 (Chaperon *et al.*, 1998) as well as delta^9-THC (Sanudo-Pena *et al.*, 1997). The cannabinoid antagonist, SR 141716, counteracted these aversive effects.

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The conditioned place preference (CPP) test also functions as a predictor of reinforcing effects. Animals show CPP to cannabinoids, but only at mid-dose levels. However, cannabinoid antagonists also induce CPP, suggesting that occupation of the cannabinoid receptor itself, may be responsible.

• Drug Discrimination Studies

Animals, including monkeys and rats (Gold *et al.*, 1992) as well as humans (Chait, 1988) can discriminate cannabinoids from other drugs or placebo. Discriminative stimulus effects of delta[9]-THC are pharmacologically specific for marijuana-containing cannabinoids (Balster and Prescott, 1992, Barrett *et al.*, 1995, Browne and Weissman, 1981, Wiley *et al.*, 1993, Wiley *et al.*, 1995). Additionally, the major active metabolite of delta[9]-THC, 11-OH-delta[9]-THC, also generalized to the stimulus cue elicited by delta[9]-THC (Browne and Weissman, 1981). Twenty-two other cannabinoids found in marijuana also fully substituted for delta[9]-THC. The discriminative stimulus effects of the cannabinoid group appear to provide unique effects because stimulants, hallucinogens, opioids, benzodiazepines, barbiturates, NMDA antagonists and antipsychotics have not been shown to substitute for delta[9]-THC.

PHARMACODYNAMICS OF CNS EFFECTS

Psychoactive effects occur within seconds after smoking marijuana, while the onset of effects after oral administration is 30-60 min. After a single moderate smoked dose, most mental and behavioral effects are measurable for approximately 4 to 6 hours (Hollister 1986, 1988). Venous blood levels of delta[9]-THC or other cannabinoids correlate poorly with intensity of effects and character of intoxication (Agurell *et al.* 1986; Barnett *et al.* 1985; Huestis *et al.* 1992a). There does not appear to be a "hangover" syndrome following acute administration of marijuana containing 2.1% delta[9]-THC (Chait, 1985).

We agree with the petitioner that clinical studies do not demonstrate tolerance to the "high" from marijuana. This may be related to recent electrophysiological data showing that the ability of THC to increase neuronal firing in the ventral tegmental area (a region known to play a critical role in drug reinforcement and reward) is not reduced following chronic administration of the drug (Wu and French, 2000). On the other hand, tolerance can develop in humans to marijuana-induced cardiovascular and autonomic changes, decreased intraocular pressure, sleep and sleep EEG, mood and certain behavioral changes (Jones et al., 1981).

Repeated use of many drugs leads to the normal physiological adaptations of tolerance and dependence and is not a phenomenon unique to drugs of abuse. Down-regulation of cannabinoid receptors has been suggested as the mechanism underlying tolerance to the effects of marijuana (Rodriguez de Fonseca *et al.*, 1994, Oviedo *et al.*, 1993). By pharmacological definition, tolerance does not indicate the physical dependence liability of a drug.

Physical dependence is a condition resulting from the repeated consumption of certain drugs. Discontinuation of the drug results in withdrawal signs and symptoms known as withdrawal or abstinence syndrome. It is believed that the withdrawal syndrome probably reflects a rebound of certain physiological effects that were altered by the repeated administration of the drug. These

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pharmacological events of physical dependence and withdrawal are not associated uniquely with drugs of abuse. Many medications such as antidepressants, beta-blockers and centrally acting antihypertensive drugs that are not associated with addiction can produce these effects after abrupt discontinuation.

Some authors describe a marijuana withdrawal syndrome consisting of restlessness, irritability, mild agitation, insomnia, sleep EEG disturbances, nausea and cramping that resolves in days (Haney et al., 1999). This syndrome is mild compared to classical alcohol and barbiturate withdrawal phenomena, which may include agitation, paranoia, and seizures. Marijuana withdrawal syndrome has more frequently been reported in adolescents who were admitted for substance abuse treatment or under research conditions upon discontinuation of daily administration.

According to the American Psychiatric Association, Diagnostic and Statistical Manual (DSM-IV-TR™, 2000), the distinction between occasional use of cannabis and cannnabis dependence or abuse can be difficult to make because social, behavioral, or psychological problems may be difficult to attribute to the substance, especially in the context of use of other substances. Denial of heavy use is common, and people appear to seek treatment for cannabis dependence or abuse less often than for other types of substance –related disorders.

Although pronounced withdrawal symptoms can be provoked from the administration of a cannabinoid antagonist in animals who had received chronic THC administration, there is no overt withdrawal syndrome behaviorally in animals under conditions of natural discontinuation following chronic THC administration. This may be the result of slow release of cannabinoids from adipose storage, as well as the presence of the major metabolite, 11-OH-delta^9-THC, which is also psychoactive.

COGNITIVE EFFECTS

Acute administration of smoked marijuana impairs performance on tests of learning, associative processes, and psychomotor behavior (Block et al., 1992). These data demonstrate that the short-term effects of marijuana can interfere significantly with an individual's ability to learn in the classroom or to operate motor vehicles. Administration of 290 ug/kg delta^9-THC in a smoked marijuana cigarette by human volunteers impaired perceptual motor speed and accuracy, two skills that are critical to driving ability (Kurzthaler et al., 1999). Similarly, administration of 3.95% delta^9-THC in a smoked marijuana cigarette increased dysequilibrium measures as well as the latency in a task of simulated vehicle braking at a rate comparable to an increase in stopping distance of 5 feet at 60 mph (Liguori et al., 1998).

The effects of marijuana may not resolve fully until at least a day after the acute psychoactive effects have subsided. A study at the National Institute on Drug Abuse (NIDA) showed residual impairment on memory tasks 24 hours after volunteer subjects had smoked 0, 1, or 2 marijuana cigarettes containing 2.57% delta^9-THC on two occasions the previous day (Heishman et al., 1990). However, later studies at NIDA showed that there were no residual alterations in subjective or performance measures the day after subjects were exposed to 1.8%, or 3.6% smoked delta^9-THC, indicating that the residual effects of smoking a single marijuana cigarette

are minimal (Fant et al., 1998). A John Hopkins study examined marijuana's effects on cognition on 1,318 participants over a 15-year period and reported there were no significant differences in cognitive decline between heavy users, light users, and nonusers of cannabis, nor any male-female differences. The authors concluded that "these results ... seem to provide strong evidence of the absence of a long-term residual effect of cannabis use on cognition." (Lyketsos et al., 1999).

Age of first use may be a critical factor in persistent impairment resulting from chronic marijuana use. Individuals with a history of marijuana-only use that began before the age of 16 were found to perform more poorly on a visual scanning task measuring attention than individuals who started using marijuana after that age (Ehrenreich et al., 1999). However, the majority of early-onset marijuana users do not go on to become heavy users of marijuana, and those that do tend to associate with delinquent social groups (Kandel and Chen, 2000).

An individual's drug history may play a role in the response that person has to marijuana. Frequent marijuana users (greater than 100 times) were better able to identify a drug effect from low dose delta^9-THC than infrequent users (less than 10 times) and were less likely to experience sedative effects from the drug (Kirk and deWit, 1999). This difference in experiential history may account for data showing that reaction times are not altered by acute administration of marijuana in long term marijuana users (Block and Wittenborn, 1985), suggesting that behavioral adaptation or tolerance can occur to the acute effects of the drug in the absence of evidence for dependence.

The impact of *in utero* marijuana exposure on a series of cognitive tasks had been studied in children at different stages of development. Differences in several cognitive domains distinguished the 4-year-old children of heavy marijuana users. In particular, memory and verbal measures were negatively associated with maternal marijuana use (Fried and Watkinson, 1987). Maternal marijuana use was predictive of poorer performance on abstract/visual reasoning tasks, although it was not associated with an overall lowered IQ in 3-year old children (Griffith *et al.*, 1994). At 6 years of age, prenatal marijuana history was associated with an increase in omission errors on a vigilance task, possibly reflecting a deficit in sustained attention, was noted (Fried *et al.*, 1992). Recently, it had been speculated that prenatal exposure may affect certain behaviors and cognitive abilities that fall under the construct termed executive function, that is, not associated with measures of global intelligence. It was postulated that when tests evaluate novel problem-solving abilities as contrasted to knowledge, there is an association between executive function and intelligence. In a recent study (Fried *et al.*, 1998), the effect of prenatal exposure in 9-12 year old children was analyzed, and similarly to what was shown in other age groups, *in utero* marijuana exposure was negatively associated with executive function tasks that require impulse control, visual analysis and hypothesis testing and it was not associated with global intelligence.

CARDIOVASCULAR AND AUTONOMIC EFFECTS

Single smoked or oral doses of delta^9-THC ingestion produce tachycardia and unchanged or increased blood pressure (Capriotti et al., 1988, Benowitz and Jones, 1975). However, prolonged delta^9-THC ingestion produces significant heart rate slowing and blood pressure lowering

(Benowitz and Jones, 1975). Both plant-derived cannabinoids and the endogenous ligands have been shown to elicit hypotension and bradycardia via activation of peripherally located CB_1 receptors (Wagner et al., 1998). The mechanism of these effects were suggested in that study to include presynaptic CB_1 receptor mediated inhibition of norepinephrine release from peripheral sympathetic nerve terminals, with the possibility of additional direct vasodilation via activation of vascular cannabinoid receptors.

Impaired circulatory responses to standing, exercise, Valsalva maneuver, and cold pressor testing following THC administration suggest a state of sympathetic insufficiency. Tolerance developed to the orthostatic hypotension, possibly related to plasma volume expansion, but did not develop to the supine hypotensive effects. During chronic marijuana ingestion, nearly complete tolerance was shown to have developed to the tachycardia and psychological effects when subjects were challenged with smoked marijuana. Electrocardiographic changes were minimal despite the large cumulative dose of THC. (Benowitz and Jones, 1975)

Cardiovascular effects of smoked or oral marijuana have not been shown to result in any health problems in healthy and relatively young users. However, marijuana smoking by older patients, particularly those with some degree of coronary artery or cerebrovascular disease, is postulated to pose greater risks, because of the resulting increased cardiac work, increased catecholamines, carboxyhemoglobin, and postural hypotension (Benowitz and Jones 1981; Hollister 1988).

As a comparison, the cardiovascular risks associated with use of cocaine are quite serious, including cardiac arrhythmias, myocardial ischemia, myocarditis, aortic dissection, cerebral ischemia, stroke and seizures.

RESPIRATORY EFFECTS

Transient bronchodilation is the most typical effect following acute exposure to marijuana. The petitioner is correct that marijuana does not suppress respiration in a manner that leads to death. With long-term use of marijuana, there can be an increased frequency of pulmonary illness from chronic bronchitis and pharyngitis. Large-airway obstruction, as evident on pulmonary function tests, can also occur with chronic marijuana smoking, as can cellular inflammatory histopathological abnormalities in bronchial epithelium (Adams and Martin 1996; Hollister 1986).

The low incidence of carcinogenicity may be related to the fact that intoxication from marijuana does not require large amounts of smoked material. This may be especially true today since marijuana has been reported to be more potent now than a generation ago and individuals typically titrate their drug consumption to consistent levels of intoxication.

Several cases of lung cancer in young marijuana users with no history of tobacco smoking or other significant risk factors have been reported (Fung et al. 1999). However, a recent study (Zhang et al., 1999) has suggested that marijuana use may dose-dependently interact with mutagenic sensitivity, cigarette smoking and alcohol use to increase the risk of head and neck cancer. The association of marijuana use with carcinomas remains controversial.

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ENDOCRINE SYSTEM EFFECTS

In male human volunteers, neither smoked THC (18 mg/marijuana cigarette) nor oral THC (10 mg t.i.d. for 3 days and on the morning of the fourth day) altered plasma prolactin, ACTH, cortisol, luteinizing hormone or testosterone levels (Dax et al., 1989). Reductions in male fertility by marijuana are reversible and only seen in animals at concentrations higher than those found in chronic marijuana users.

Relatively little research has been performed on the effects of experimentally administered marijuana on human female endocrine and reproductive system function. Although suppressed ovulation and other ovulatory cycle changes occur in nonhuman primates, a study of human females smoking marijuana in a research hospital setting did not find hormone or menstrual cycle changes like those in monkeys that had been given delta^9-THC (Mendelson et al., 1984a).

THC reduces binding of the corticosteroid dexamethasone in hippocampal tissue from adrenalectomized rats, suggesting a direct interaction with the glucocorticoid receptor. Chronic THC administration also reduced the number of glucocorticoid receptors. Acute THC releases corti-costerone, but tolerance developed with chronic THC administration. (Eldridge et al., 1991)

IMMUNE SYSTEM EFFECTS

Immune functions can be enhanced or diminished by cannabinoids, dependent on experimental conditions, but the effects of endogenous cannabinoids on the immune system are not yet known. The concentrations of THC that are necessary for psychoactivity are lower than those that alter immune responses.

A study presented by Abrams and coworkers at the University of California, San Francisco at the XIII International AIDS Conference investigated the effect of marijuana on immunological functioning in 62 AIDS patients who were taking protease inhibitors. Subjects received one of three treatments, three times a day: smoked marijuana cigarette containing 3.95% THC; oral tablet containing THC (2.5 mg oral dronabinol); or oral placebo. There were no changes in HIV RNA levels between groups, demonstrating no short-term adverse virologic effects from using cannabinoids. Additionally, those individuals in the cannabinoid groups gained more weight than those in the placebo group (3.51 kg from smoked marijuana, 3.18 kg from dronabinol, 1.30 kg from placebo) (7/13/00, Durban, South Africa).

3.   THE STATE OF CURRENT SCIENTIFIC KNOWLEDGE REGARDING THE DRUG OR OTHER SUBSTANCE

This section discusses the chemistry, human pharmacokinetics, and medical uses of marijuana.

CHEMISTRY

According to the DEA, three forms of cannabis (that is, Cannabis sativa L. and other species) are currently marketed illicitly in the U.S.A. These cannabis derivatives include marijuana, hashish and hashish oil.

Each of these forms contains a complex mixture of chemicals. Among these components the twenty-one carbon terpenes found in the plant as well as their carboxylic acids, analogues, and transformation products are known as cannabinoids (Agurell et al., 1984, 1986; Mechoulam, 1973). The cannabinoids appear to be unique to marijuana and most of the naturally-occurring have been identified. Among the cannabinoids, delta^9-tetrahydrocannabinol (delta^9-THC, alternate name delta^1-THC) and delta-8-tetrahydrocannabinol (delta^8-THC, alternate name delta^6-THC) are the only compounds in the plant, which show all of the psychoactive effects of marijuana. Because delta^9-THC is more abundant than delta^8-THC, the activity of marijuana is largely attributed to the former, which is considered the main psychoactive cannabinoid in cannabis. Delta^8-THC is found only in few varieties of the plant (Hively et al., 1966). Other cannabinoids, such as cannabidiol (CBD) and cannabinol (CBN), has been characterized. CBD is not considered to have cannabinol-like psychoactivity, but is thought to have significant anticonvulsant, sedative, and anxiolytic activity (Adams and Martin, 1996; Agurell et al., 1984, 1986; Hollister, 1986).

Marijuana is a mixture of the dried flowering tops and leaves from the plant (Agurell et al. 1984; Graham 1976; Mechoulam 1973) and is variable in content and potency (Agurell et al. 1986; Graham 1976; Mechoulam 1973). Marijuana is usually smoked in the form of rolled cigarettes. The other cannabis forms are also smoked. Potency of marijuana, as indicated by cannabinoid content, has been reported to average from as low as one to two percent to as high as 17 percent.

Delta^9-THC is an optically active resinous substance, insoluble in water and extremely lipid soluble. Chemically is known as (6aR-*trans*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo-[b,d]pyran-1-ol or (-)-delta^9-(*trans*)-tetrahydrocannabinol. The pharmacological activity of delta^9-THC is stereospecific; the (-)-*trans* isomer is 6-100 times more potent than the (+)-*trans* isomer (Dewey et al., 1984).

The concentration of delta^9-THC and other cannabinoids in marijuana varies greatly depending on growing conditions, parts of the plant collected (flowers, leaves stems, etc), plant genetics, and processing after harvest (Adams and Martin, 1996; Agurell et al., 1984; Mechoulam, 1973). Thus, there are many variables that can influence the strength, quality and purity of marijuana as a botanical substance. In the usual mixture of leaves and stems distributed as marijuana, the concentration of delta^9-THC ranges from 0.3 to 4.0 percent by weight. However, specially grown and selected marijuana can contain 15 percent or even more delta^9-THC. Thus, a one-gram marijuana cigarette might contain as little as 3 milligrams or as much as 150 milligrams or more of delta^9-THC among several other cannabinoids. As a consequence, the clinical pharmacology of pure delta^9-THC may not always be expected to have the same clinical pharmacology of smoked marijuana containing the same amount of delta^9-THC (Harvey, 1985). Also, the lack of consistency of concentration of delta^9-THC in botanical marijuana from diverse sources makes the interpretation of clinical data very difficult. If marijuana is to be investigated more widely for medical use, information and data regarding the chemistry, manufacturing and specifications of marijuana must be developed. 21 C.F.R. § 314.50 (d) (1) describes the data and information that should be included in.the chemistry, manufacturing and controls section of a new drug application (NDA) to be reviewed by FDA.

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Hashish consists of the cannabinoid-rich resinous material of the cannabis plant, which is dried and compressed into a variety of forms (balls, cakes etc.). Pieces are then broken off, placed into pipes and smoked. Cannabinoid content in hashish has recently been reported by DEA to average 6 percent.

Hash oil is produced by extracting the cannabinoids from plant material with a solvent. Color and odor of the extract vary, depending on the type of solvent used. Hash oil is a viscous brown or amber-colored liquid that contains approximately 15 percent cannabinoids. One or two drops of the liquid placed on a cigarette purportedly produce the equivalent of a single marijuana · cigarette.

HUMAN PHARMACOKINETICS

Marijuana is generally smoked as a cigarette (weighing between 0.5 and 1.0 gram), or in a pipe. It can also be taken orally in foods or as extracts of plant material in ethanol or other solvents. Pure preparations of delta^9-THC and other cannabinoids can be administered by mouth, rectal suppository, intravenous injection, or smoked.

The absorption, metabolism, and pharmacokinetic profile of delta^9-THC (and other cannabinoids) in marijuana or other drug products containing delta^9-THC are determined by route of administration and formulation (Adams and Martin 1996; Agurell et al. 1984, 1986). When marijuana is administered by smoking, delta^9-THC in the form of an aerosol in the inhaled smoke is absorbed within seconds. The delta^9-THC is delivered to the brain rapidly and efficiently as would be expected of a very lipid-soluble drug. The delta^9-THC bioavailability from smoked marijuana, i.e., the actual absorbed dose as measured in blood, varies greatly among individuals. Bioavailability can range from one percent to 24 percent with the fraction absorbed rarely exceeding 10 to 20 percent of the delta^9-THC in a marijuana cigarette or pipe (Agurell et al. 1986; Hollister 1988a). This relatively low and quite variable bioavailability results from significant loss of delta^9-THC in side-stream smoke, from variation in individual smoking behaviors, from cannabinoid pyrolysis, from incomplete absorption of inhaled smoke, and from metabolism in the lungs. A smoker's experience is likely an important determinant of the dose that is actually absorbed (Herning et al. 1986; Johansson et al. 1989). Venous blood levels of delta^9-THC or other cannabinoids correlate poorly with intensity of effects and character of intoxication (Agurell et al. 1986; Barnett et al. 1985; Huestis et al. 1992a).

After smoking, venous levels of delta^9-THC decline precipitously within minutes, and within an hour are about 5 to 10 percent of the peak level (Agurell et al., 1986, Huestis et al., 1992a, 1992b). Plasma clearance of delta^9-THC is approximately 950 mL/min or greater, thus approximating hepatic blood flow. The rapid disappearance of delta^9-THC from blood is largely due to redistribution to other tissues in the body, rather than to metabolism (Agurell et al., 1984, 1986). Metabolism in most tissues is relatively slow or absent. Slow release of delta^9-THC and other cannabinoids from tissues and subsequent metabolism results in a long elimination half-life. The terminal half-life of delta^9-THC is estimated to range from approximately 20 hours to as long as 10 to 13 days, though reported estimates vary as expected with any slowly cleared substance and the use of assays of variable sensitivities.

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In contrast, following an oral dose of delta^9-THC or marijuana, maximum delta^9-THC and other cannabinoid blood levels are attained after 2 to 3 hours (Adams and Martin 1996; Agurell *et al.* 1984, 1986). Oral bioavailability of delta^9-THC, whether pure or in marijuana, is low and extremely variable, ranging between 5 and 20 percent (Agurell *et al.* 1984, 1986). There is inter- and intra-subject variability, even when repeatedly dosed under controlled and ideal conditions. The low and variable oral bioavailability of delta^9-THC is a consequence of its first-pass hepatic elimination from blood and erratic absorption from stomach and bowel. Because peak effects are slow in onset, typically one or two hours after an oral dose, and variable in intensity, it is more difficult for a user to titrate the oral delta^9-THC dose than with marijuana smoking. When smoked, the active metabolite, 11-hydroxy-delta^9-THC, probably contributes little to the effects since relatively little is formed, but after oral administration, metabolite levels produced may exceed that of delta^9-THC and thus contribute greatly to the pharmacological effects of oral delta^9-THC or marijuana. Delta^9-THC is metabolized via microsomal hydroxylation to more than 80, active and inactive, metabolites (Lemberger *et al.*, 1970, Lemberger *et al.*, 1972a, 1972b) of which the primary active metabolite was 11-OH-delta^9-THC. This metabolite is approximately equipotent to delta^9-THC in producing marijuana-like subjective effects (Agurell *et al.*, 1986, Lemberger and Rubin, 1975). Following oral administration of radioactive-labeled delta^9-THC, it has been confirmed that delta^9-THC plasma levels attained by the oral route are low relative to those levels after smoking or intravenous administration. The half-life of delta^9-THC has been determined to be 23-28 hours in heavy marijuana users, but 60-70 hours in naive users (Lemberger *et al.*, 1970).

Characterization of the pharmacokinetics of delta^9-THC and other cannabinoids from smoked marijuana is difficult (Agurell *et al.*, 1986, Herning *et al.*, 1986, Heustis *et al*, 1992a) in part because a subject's smoking behavior during an experiment cannot be easily controlled or quantified by the researcher. An experienced marijuana smoker can titrate and regulate the dose to obtain the desired acute psychological effects and to avoid overdose and/or minimize undesired effects. Each puff delivers a discrete dose of delta^9-THC to the body. Puff and inhalation volume changes with phase of smoking, tending to be highest at the beginning and lowest at the end of smoking a cigarette. Some studies found frequent users to have higher puff volumes than less frequent marijuana users. During smoking, as the cigarette length shortens, the concentration of delta^9-THC in the remaining marijuana increases; thus, each successive puff contains an increasing concentration of delta^9-THC.

Cannabinoid metabolism is extensive. There are at least 80 probable biologically inactive, but not completely studied, metabolites formed from delta^9-THC (Agurell *et al.*, 1986; Hollister, 1988a). In addition to the primary active metabolite, 11-hydroxy-delta^9-THC, some inactive carboxy metabolites have terminal half-lives of 50 hours to 6 days or more. The latter substances serve as long term markers of earlier marijuana use in urine tests. Most of the absorbed delta^9-THC dose is eliminated in feces, and about 33 percent in urine. Delta^9-THC enters enterohepatic circulation and undergoes hydroxylation and oxidation to 11-nor-9-carboxy-delta^9-THC. The glucuronide is excreted as the major urine metabolite along with about 18 nonconjugated metabolites. Frequent and infrequent marijuana users are similar in the way they metabolize delta^9-THC (Agurell *et al.*, 1986). `

FDA has not approved a new drug application for marijuana, although there are several INDs currently active. There is suggestive evidence that marijuana may have beneficial therapeutic effects in relieving spasticity associated with multiple sclerosis, as an analgesic, as an antiemetic, as an appetite stimulant and as a bronchodilator, but there is no data from controlled clinical trials to support a new drug application for any of these indications. Data of the risks and potential benefits of using marijuana for these various indications must be developed to determine whether botanical marijuana, or any cannabinoid in particular, has a therapeutic role.

In February 1997, a NIH-sponsored workshop analyzed available scientific information and concluded that "in order to evaluate various hypotheses concerning the potential utility of marijuana in various therapeutic areas, more and better studies would be needed" (NIH, 1997). In addition, in March 1999, the Institute of Medicine (IOM) issued a detailed report that supports the absolute need for evidence-based research into the effects of marijuana and cannabinoid components of marijuana, for patients with specific disease conditions. The IOM report also emphasized that smoked marijuana is a crude drug delivery system that exposes patients to a significant number of harmful substances and that "if there is any future for marijuana as a medicine, it lies in its isolated components, the cannabinoids and their synthetic derivatives." As such, the IOM recommended that clinical trials should be conducted with the goal of developing safe delivery systems (Institute of Medicine, 1999). Additionally, State-level public initiatives, including referenda in support of the medical use of marijuana have generated interest in the medical community for high quality clinical investigation and comprehensive safety and effectiveness data.

The Department of Health and Human Services (DHHS) is committed to providing "research-grade marijuana for studies that are the most likely to yield usable, essential data" (DHHS, 1999). The opportunity for scientists to conduct clinical research with botanical marijuana has increased due to changes in the process for obtaining botanical marijuana from the National Institute on Drug Abuse, the only legal source of the drug for research. Studies published in the current medical literature demonstrate that clinical research with marijuana is being conducted in the US under FDA-authorized Investigational New Drug applications. In May 1999, DHHS provided guidance on the procedures for providing research-grade marijuana to scientists who intend to study marijuana in scientifically valid investigations and well-controlled clinical trials (DHHS, 1999). This action was prompted by the increasing interest in determining through scientifically valid investigations whether cannabinoids have medical use.

4. ITS HISTORY AND CURRENT PATTERN OF ABUSE

To assess drug abuse patterns and trends, data from different sources such as National Household Survey on Drug Abuse (NHSDA), Monitoring the Future (MTF), Drug Abuse Warning Network (DAWN), and Treatment Episode Data Set (TEDS) have been analyzed. These indicators of marijuana use in the United States are described below:

The National Household Survey on Drug Abuse (NHSDA, 1999) is conducted by the Department of Health and Human Service's Substance Abuse and Mental Health Services Administration (SAMHSA) annually. This survey has been the primary source of estimates of the prevalence and incidence of alcohol, tobacco and illicit drug use in the US. It is important to note that this survey identifies whether an individual used a drug during a certain period, but not the amount of the drug used on each occasion. The survey is based on a nationally representative sample of the civilian, non-institutionalized population 12 years of age and older. Persons excluded from the survey include homeless people who do not use shelters, active military personnel, and residents of institutional group quarters, such as jails and hospitals. In 1999, 66,706 individuals were interviewed.

According to the 1999 NHSDA, illicit drug use involved approximately 14.8 million Americans (6.7% of the US population) on a monthly basis. The most frequently used illicit drug was marijuana, with 11.2 million Americans (5.1% of the US population) using it monthly. The 1999 NHSDA no longer provides data on the weekly or daily use of any drug, so these statistics are unavailable for marijuana. The NHSDA estimated that 76.4 million Americans (34.6% of the population) have tried marijuana at least once during their lifetime. Thus, 14.7% of those who try marijuana go on to use it monthly. NHSDA data from 1999 show that 57% of illicit drug users only use marijuana on a monthly basis, which corresponds to 8.44 million persons (3.8% of the US population). However, there are no data available on marijuana-only use as a percent of use of any drug.–

An estimated 2.3 million persons of all ages used marijuana for the first time in 1998, of whom 1.6 million were between the ages of 12-17. (Information on when people first used a substance is collected on a retrospective basis, so this information is always one year behind information on current use.) This represents a slight reduction in new marijuana users from 1997, when the rate was 2.6 million people of all ages and 1.8 million for those 12-17 years old. Trends for marijuana use were similar to the trends for any illicit use. There were no significant changes between 1998 and 1999 for any of the four age groups, but an increasing trend since 1997 among young adults age 18-25 years (12.8 % in 1997, 13.8 % in 1998, and 16.4 % in 1999) and a decreasing trend since 1997 for youths age 12-17 years (9.4 % in 1997, 8.3 % in 1998, and 7.0 % in 1999).

MONITORING THE FUTURE

Monitoring the Future (MTF, 1999) is a national survey that tracks drug use trends among American adolescents. The MTF has surveyed 8th, 10th and 12th graders every spring in randomly selected U.S. schools since 1975 for 12th graders and since 1991 for 8th and 10th graders. This survey is conducted by the Institute for Social Research at the University of Michigan under a grant from NIDA. The 1999 sample sizes were 17,300, 13,900, and 14,100 in 8th, 10th, and 12th grades, respectively. In all, about 45,000 students in 433 schools participated. Because multiple questionnaire forms are administered at each grade level, and because not all questions are contained in all forms, the numbers of cases upon which a particular statistic are based can be less than the total sample.

Comparisons between the MTF and students sampled in the NHSDA (described above) have generally shown NHSDA prevalence to be lower than MFT estimates, in which the largest difference occurred with 8th graders. The MTF survey showed the use of illegal drugs by adolescents leveled off in 1997 and then declined somewhat for most drugs in 1998. Also, the 1998-year survey showed that for the first time since 1991 an increase in the percentage of 8th graders who said marijuana is a risk to their health.

Illicit drug use among teens remained steady in 1999 in all three grades, as did the use of a number of important specific drugs such as marijuana, amphetamines, hallucinogens taken as a class, tranquilizers, heroin, and alcohol. Marijuana is the most widely used illicit drug. For 1999, the annual prevalence rates in grades 8, 10, and 12, respectively, are 17%, 32%, and 38%. Current monthly prevalence rates are 9.7%, 19.4% and 23.1%. (See Table 1), whereas current daily prevalence rates (defined as the proportion using it on 20 or more occasions in the prior thirty days) are 1.4%, 3.8%, and 6.0%.

Table 1: Trends in annual and monthly prevalence of use of various drugs for eighth, tenth, and twelfth graders. Entries are percentages.

	ANNUAL			30-DAY		
	1997	1998	1999	1997	1998	1999
ANY ILLICIT DRUG (a)						
8TH GRADE	22.1	21.0	20.5	12.9	12.1	12.2
10TH GRADE	38.5	35.0	35.9	23.0	21.5	22.1
12TH GRADE	42.4	41.4	42.1	26.2	25.6	25.9
ANY ILLICIT DRUG OTHER THAN CANNABIS (a)						
8TH GRADE	11.8	11.0	10.5	6.0	5.5	5.5
10TH GRADE	18.2	16.6	16.7	8.8	8.6	8.6
12TH GRADE	20.7	20.2	20.7	10.7	10.7	10.4
MARIJUANA/HASHISH						
8TH GRADE	17.7	16.9	16.5	10.2	9.7	9.7
10TH GRADE	34.8	31.1	32.1	20.5	18.7	19.4
12TH GRADE	38.5	37.5	37.8	23.7	22.8	23.1
COCAINE						
8TH GRADE	2.8	3.1	2.7	1.1	1.4	1.3
10TH GRADE	4.7	4.7	4.9	2.0	2.1	1.8
12TH GRADE	5.5	5.7	6.2	2.3	2.4	2.6
HEROIN (b)						
8TH GRADE	1.3	1.3	1.4	0.6	0.6	0.6
10TH GRADE	1.4	1.4	1.4	0.6	0.7	0.7
12TH GRADE	1.2	1.0	1.1	0.5	0.5	0.5

SOURCE: The Monitoring the Future Study, the University of Michigan.

a. For 12th graders only: Use of "any illicit drug" includes any use of marijuana, LSD, other hallucinogens, crack, other cocaine, or heroin, or any use of other opiates, stimulants, barbiturates, or tranquilizers not under a doctor's orders. For 8th and 10th graders: The use of other opiates and barbiturates has been excluded, because these younger respondents appear to over-report use (perhaps because they include the use of nonprescription drugs in their answers).

b. In 1995, the heroin question was changed in three of six forms for 12th graders and in two forms for 8th and 10th graders. Separate questions were asked for use with injection and without injection. Data presented here represents the combined data from all forms. In 1996, the heroin question was changed in the remaining 8th and 10th grade forms.

DRUG ABUSE WARNING NETWORK (DAWN)

The Drug Abuse Warning Network (DAWN, 1998) is a national probability survey of hospitals with emergency departments (EDs) designed to obtain information on ED episodes that are induced by or related to the use of an illegal drug or the non-medical use of a legal drug. The DAWN system provides information on the health consequences of drug use in the United States as manifested by drug-related visits to emergency departments (ED episodes). DAWN captures the non-medical use of a substance either for psychological effects, dependence, or suicide attempt. The ED data come from a representative sample of hospital emergency department's which are weighted to produce national estimates. As stated in DAWN methodology, "the terms 'ED drug abuse episode' or 'ED episode' refer to any ED visit that was induced by or related to drug abuse. Similarly, the terms 'ED drug mention' or 'ED mention' refer to a substance that was mentioned in a drug abuse episode. Up to 4 substances can be reported for each ED episode. Thus, the number of ED mentions will always equal or exceed the number of ED episodes."

Many factors can influence the estimates of ED visits, including trends in the ED usage in general. Some drug users may have visited EDs for a variety of reasons, some of which may have been life threatening, whereas others may have sought care at the ED for detoxification because they needed certification before entering treatment. It is important to note that the variable "Motive" applies to the entire episode and since more than one drug can be mentioned per episode, it may not apply to the specific drug for which the tables have been created. DAWN data do not distinguish the drug responsible for the ED visit from others used concomitantly. The DAWN report itself states, "Since marijuana/hashish is frequently present in combination with other drugs, the reason for the ED contact may be more relevant to the other drug(s) involved in the episode."

In 1999, there were an estimated 554,932 drug-related ED episodes and 1,015,206 ED drug mentions from these drug-related episodes. Nationally, the number of ED episodes and mentions remained relatively stable from 1998 to 1999. The 4 drugs mentioned most frequently in ED reports – alcohol-in-combination (196,277 mentions), cocaine (168,763), marijuana/hashish (82,150), and heroin/morphine (84,409) – were statistically unchanged from 1998 to 1999. Marijuana/hashish mentions represented 16% of all drug-related episodes in 1999. For adolescent patients age 12-17, there was no statistical change from 1998 to 1999 in drug use for any drug category (Table 2). There was no a statistically significant change in the number of marijuana/hashish mentions, heroin/morphine of cocaine from 1998 to 1999.

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Table 2: Estimated number of emergency department drug episodes, drug mentions and mentions for selected drugs for total coterminous US by year for 1997-1999.

	1997	1998	1999
DRUG EPISODES	527,058	542,544	554,932
DRUG MENTIONS	943,937	982,856	1,015,206
COCAINE	161,087	172,014	168,763
HEROIN/MORPHINE	72,010	77,645	84,409
MARIJUANA/HASHISH	64,744	76,870	87,150

Source: Office of applied studies, SAMHSA, Drug Abuse Warning Network, 1999 (03/2000 update). Note: These estimates are based on a representative sample of non-federal, short-stay hospitals with 24-hour emergency departments in the U.S.

There were no statistically significant increases in marijuana/hashish mentions on the basis of age, gender, or race/ethnicity subgroups between 1998 and 1999, although a 19% increase in marijuana/hashish mentions (from 22,907 to 27,272) among young adults age 18 to 25 was observed.

Approximately 15 percent of the emergency department marijuana/hashish mentions involved patients in the 6-17 years of age, whereas this age group only accounts for less than 1 percent of the emergency department heroin/morphine and approximately 2 percent of the cocaine emergency department mentions. Most of the emergency department heroin/morphine and cocaine mentions involved subjects in the 26-44 years of age range.

Marijuana/hashish is likely to be mentioned in combination with other substances, particularly with alcohol and cocaine. Marijuana use as a single drug accounted for approximately 22% of the marijuana episodes. Single use of cocaine and heroin accounted for 29% and 47% of the cocaine and heroine episodes respectively.

The petitioner asserts that "common household painkillers" and benzodiazepines produce more ED visits than marijuana and that marijuana users are no more likely to be seen in EDs than other chronic drug users. DAWN data do not confirm the petitioner's assertions. For 1999, the estimated rate of mentions of selected drugs per 100,000 population is 69.4 for cocaine, 35.8 for marijuana/hashish, 34.7 for heroin/morphine, 17.5 for alprazolam/diazepam/lorazepam, and 16.9 for aspirin/acetaminophen. The estimated rate of mentions of marijuana/hashish per 100,000 population is similar to that of heroin/morphine, but approximately twice that of aspirin/acetaminophen and that of alprazolam/diazepam/ lorazepam. However, marijuana estimated rate of mentions/100,000 population is approximately half that of cocaine.

These drugs are easily distinguished by the motivation for their use. In 1999, marijuana/hashish mentions were related to episodes in which the motive for drug intake was primarily dependence (34.2%) followed by recreational use (28%), suicide (11.5%) and other psychic effects (8.1%).

DAWN defines "psychic effects" as a conscious action to use a drug to improve or enhance any physical, emotional, or social situation or condition. The use of a drug for experimentation or to enhance a social situation, as well as the use of drugs to enhance or improve any mental, emotional, or physical state, is reported to DAWN under this category. Examples of the latter include anxiety, stay awake, help to study, weight control, reduce pain and to induce sleep. A different pattern is observed for tranquilizers (alprazolam/diazepam/lorazepam) and aspirin/acetamipnophen. Alprazolam/diazepam/lorazepam mentions were primarily related to episodes where the motive for drug intake was primarily suicide (approximately 58%), followed by dependence (approximately 17%), other psychic effects (approximately 11%), and recreational use (approximately 5%). For the use of aspirin/acetaminophen the primary motive of the episode was suicide (80%), other psychic effects (9%) and recreational use (2%).

DAWN also collects information on drug-related deaths from selected medical examiner offices from more than 40 metropolitan areas. In 1997 and 1998, there were 678 and 595 marijuana-related death mentions, representing 7.1 and 5.9 percent of the total drug abuse deaths for each year respectively. Medical examiner data also showed that in the majority of the mentions, marijuana was used concomitantly with cocaine, heroin and alcohol.

TREATMENT EPISODE DATA SET

The Treatment Episode Data Set (TEDS, 1998) system is part of SAMHSA's Drug and Alcohol Services Information System (Office of Applied Science, SAMHSA). TEDS comprises data on treatment admissions that are routinely collected by States in monitoring their substance abuse treatment systems. The TEDS report provides information on the demographic and substance use characteristics of the 1.5 million annual admissions to treatment for abuse of alcohol and drugs in facilities that report to individual State administrative data systems. It is important to note that TEDS is an admission-based system, and TEDS admissions do not represent individuals, because a given individual admitted to treatment twice within a given year would be counted as two admissions. TEDS includes facilities that are licensed or certified by the State substance abuse agency to provide substance abuse treatment and that are required by the States to provide TEDS client-level data. Facilities that report TEDS data are those that receive State alcohol and/or drug agency funds for the provision of alcohol and/or drug treatment services. The primary goal for TEDS is to monitor the characteristics of treatment episodes for substance abusers.

Primary marijuana abuse accounted for 13% of TEDS admissions in 1998, the latest year for which data are available. In general, most of the individuals admitted for marijuana were white young males. Marijuana use began at an early age among primary marijuana admissions and more than half of the admitted patients had first used marijuana by the age of 14 and 92% by the age of 18. More than half of marijuana treatment admissions were referred through the criminal justice system.

Approximately one-third of those who were admitted for primary marijuana abuse use the drug daily. Between 1992 and 1998, the proportion of admissions for primary marijuana use increased from 6% to 13%, whereas the proportion of admissions for primary cocaine use declined from 18% in 1992 to 15% in 1998. The proportion of opiate admissions increased from 12% in 1992

to 15% in 1998 and alcohol accounted for about half (47%) of all TEDS admissions in 1998. Marijuana has not been associated with other drugs in 30.8 % of the primary marijuana admissions that corresponds to 4.1% of all admissions. Secondary use of alcohol was reported by 38.2 % of the marijuana admissions and secondary cocaine use was reported by 4 % of admissions for primary marijuana abuse. The combination marijuana/alcohol/cocaine accounts for 8.5 % of marijuana primary admissions and 1.1% of all admissions.

The TEDS Report concludes that, "Overall, TEDS admissions data confirm that those admitted to substance abuse treatment have problems beyond their dependence on drugs and alcohol, being disadvantaged in education and employment when compared to the general population after adjusting for age, gender, and race/ethnicity distribution differences between the general population and the TEDS. It is not possible to conclude cause and effect from TEDS data - whether substance abuse precedes or follows the appearance of other life problems - but the association between problems seems clear."

NIDA'S COMMUNITY EPIDEMIOLOGY WORK GROUP (CEWG, 1999)

The CEWG is a network composed of epidemiologic and ethnographic researchers from major metropolitan areas of the United States and selected countries from abroad that meets semiannually to discuss the current epidemiology of drug abuse. Large-scale databases used in analyses include TEDS; DAWN; the Arrestee Drug Abuse Monitoring (ADAM) program funded by the National Institute of Justice; information on drug seizures, price, and purity from the Drug Enforcement Administration; Uniform Crime Reports maintained by the Federal Bureau of Investigation and Poison Control Centers. These data are enhanced with qualitative information obtained from ethnographic research, focus groups, and other community-based sources. Although data from TEDS and DAWN have been previously discussed this document, the analysis offered by the CEWG gives a more descriptive overview of individual geographical areas. In 1999, marijuana indicators were stable in 17 of the 21 CEWG areas. Indicators were mixed in two areas (Atlanta and Baltimore) and increased in two (Los Angeles and St. Louis). Despite the stability of certain indicators, marijuana abuse remains a serious problem in CEWG areas. In Atlanta, marijuana is the second most prevalent drug on the market and is increasingly used by a wide variety of people mostly white males and young adolescents. In St. Louis, marijuana indicators are increasing and DAWN marijuana ED mentions rose 33.3 % from the last half of 1998 to the first half of 1999. Treatment admissions rose 40.1 % from the second half of 1998 to the first half of 1999, and another 9.6 % in the second half of 1999.

In recent years, the proportion of primary marijuana abusers entering drug abuse treatment programs has been increasing in many CEWG cities. For example, between 1998 and the first semester of 1999, drug treatment admissions for primary marijuana abuse increased from 15.2 % to 20.3 % in Atlanta. In the first half of 1999, primary marijuana abusers represented 18.8 % of drug treatment admissions in New York City compared with 16.6 % in the first half of 1998. In the first half of 1999, primary marijuana abuse represented 41.2 % of all drug treatment admissions in Denver and totaled 3,179. The number of primary marijuana admissions in St. Louis increased dramatically in the first half of 1999, representing 40.8 % of treatment admissions.

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The CEWG reports an increase in problems associated with marijuana that they attribute to the drug's greater availability/potency, its relative low cost, and a public attitude that use of marijuana is less risky than use of other drugs.

5.   THE SCOPE, DURATION, AND SIGNIFICANCE OF ABUSE

According to the National Household Survey on Drug Abuse and the Monitoring the Future study, marijuana remains the most extensively used illegal drug in the US, with 34.6% of individuals over age 12 (76.4 million) and 49.7% of 12th graders having tried it at least once in their lifetime. While the majority of individuals (85.3%) who have tried marijuana do not use the drug monthly, 11.2 million individuals (14.7%) report that they used marijuana within the past 30 days. An examination of use among various age cohorts demonstrates that monthly use occurs primarily among college age individuals, with use dropping off sharply after age 25.

The Drug Abuse Warning Network data show that among 18-25 year olds, there was a 19% increase in 1999 for marijuana emergency department mentions. The fact that this age cohort had the greatest degree of acute adverse reactions to marijuana might be expected given that this group has the largest prevalence of marijuana use. Marijuana was commonly associated with alcohol and cocaine.

According to 1999 DAWN data, there were 187 deaths mentions where marijuana was the only drug reported, out of the total 664 medical examiners episodes involving marijuana in 1999. In the majority of the medical examiners episodes marijuana was associated with alcohol, cocaine, and morphine.

Data from the Treatment Episode Data Set confirm that 69 % of admissions to drug treatment programs for primary marijuana abuse also had concurrent use of alcohol and other drugs. The TEDS report also emphasizes that individuals who are admitted for drug treatment have multiple disadvantages in education and employment compared to the general population. Individuals most likely to develop dependence on marijuana have a higher rate of associated psychiatric disorders or are socializing with a delinquent crowd.

6.   ·   WHAT, IF ANY, RISK THERE IS TO THE PUBLIC HEALTH

The risk to the public health as measured by quantifiers such as emergency room episodes, marijuana-related deaths, and drug treatment admissions is discussed in full in sections 1, 4, and 5 above. Accordingly, this section focuses on the health risks to the individual user. All drugs, both medicinal and illicit, have a broad range of effects on the individual user that are dependent on dose and duration of usage. It is not uncommon for a FDA approved drug product to produce adverse effects even at doses in the therapeutic range. Such adverse responses are known as "side effects". When determining whether a drug product is safe and effective for any indication, FDA performs a thorough risk-benefit analysis to determine whether the risks posed by the drug product's potential or actual side effects are outweighed by the drug product's potential benefits. As marijuana is not approved for any use, any potential benefits attributed to marijuana use have not been found to be outweighed by the risks. However, cannabinoids have a remarkably low

acute lethal toxicity despite potent psychoactivity and pharmacologic actions on multiple organ systems.

The consequences of marijuana use and abuse are discussed below in terms of the risk from acute and chronic use of the drug to the individual user (IOM, 1999) (see also the discussion of the central nervous system effects, cognitive effects, cardiovascular and autonomic effects, respiratory effects, and the effect on the immune system in Section 2):

Risks from acute use of marijuana:

Acute use of marijuana causes an impairment of psychomotor performance, including performance of complex tasks, which makes it inadvisable to operate motor vehicles or heavy equipment after using marijuana. People who have or are at risk of developing psychiatric disorders may be the most vulnerable to developing dependence on marijuana. Dysphoria is a potential response in a minority of individuals who use marijuana.

Risks from chronic use of marijuana:

Marijuana smoke is considered to be comparable to tobacco smoke in respect to increased risk of cancer, lung damage, and poor pregnancy outcome. An additional concern includes the potential for dependence on marijuana, which has been assessed to be rare among the general population but more common among adolescents with conduct disorder and individuals with psychiatric disorders. Although a distinctive marijuana withdrawal syndrome has been identified, it is mild and short-lived.

The Diagnostic and Statistical Manual (DSM-IV-SR, 2000) of American Psychiatric Association states that the consequences of cannabis abuse are as follows:

> [P]eriodic cannabis use and intoxication can interfere with performance at work or school and may be physically hazardous in situations such as driving a car. Legal problems may occur as a consequence of arrests for cannabis possession. There may be arguments with spouses or parents over the possession of cannabis in the home or its use in the presence of children. When psychological or physical problems are associated with cannabis in the context of compulsive use, a diagnosis of Cannabis Dependence, rather than Cannabis Abuse, should be considered.
>
> Individuals with Cannabis Dependence have compulsive use and associated problems. Tolerance to most of the effects of cannabis has been reported in individuals who use cannabis chronically. There have also been some reports of withdrawal symptoms, but their clinical significance is uncertain. There is some evidence that a majority of chronic users of cannabinoids report histories of tolerance or withdrawal and that these individuals evidence more severe drug-related problems overall. Individuals with Cannabis Dependence may use very potent cannabis throughout the day over a period of months or years, and they may spend several hours a day acquiring and using the substance. This often

interferes with family, school, work, or recreational activities. Individuals with Cannabis Dependence may also persist in their use despite knowledge of physical problems (e.g., chronic cough related to smoking) or psychological problems (e.g., excessive sedation and a decrease in goal-oriented activities resulting from repeated use of high doses).

7. ITS PSYCHIC OR PHYSIOLOGIC DEPENDENCE LIABILITY

Tolerance can develop to marijuana-induced cardiovascular and autonomic changes, decreased intraocular pressure, sleep and sleep EEG, mood and behavioral changes (Jones *et al.*, 1981). Down-regulation of cannabinoid receptors has been suggested as the mechanism underlying tolerance to the effects of marijuana (Rodriguez de Fonseca *et al.*, 1994). Pharmacological tolerance does not indicate the physical dependence liability of a drug.

In order for physical dependence to exist, there must be evidence for a withdrawal syndrome. Although pronounced withdrawal symptoms can be provoked from the administration of a cannabinoid antagonist in animals who had received chronic THC administration, there is no overt withdrawal syndrome behaviorally in animals under conditions of natural discontinuation following chronic THC administration. The marijuana withdrawal syndrome is distinct but mild compared to the withdrawal syndromes associated with alcohol and heroin use, consisting of symptoms such as restlessness, mild agitation, insomnia, nausea and cramping that resolve after 4 days (Budney *et al.*, 1999; Haney *et al.*, 1999). These symptoms are comparable to the decreased vigor, increased fatigue, sleepiness, headache, and reduced ability to work seen with caffeine withdrawal (Lane *et al.*, 1998). However, marijuana withdrawal syndrome has only been reported in adolescents who were inpatients for substance abuse treatment or in individuals who had been given marijuana on a daily basis during research conditions. Physical dependence on marijuana is a rare phenomenon compared to other psychoactive drugs and if it develops, it is milder when marijuana is the only drug instead of being used in combination with other drugs.

TEDS data for 1998 show that 37.9% of admissions for treatment for primary marijuana use met DSM IV criteria for cannabis dependence, whereas 27.7 % met DSM IV criteria for cannabis abuse. Taken in the context of the total number of admissions, a DSM IV diagnosis for cannabis dependence represented 6.6 %, and a diagnosis for cannabis abuse represented 4.9 %, of all subjects admitted to treatment. In contrast, opioid and cocaine dependence was the DSM diagnosis of 12.2 % and 12.6 % of all admissions, respectively. (See Section 6 regarding marijuana abuse and dependence). ·

According to the NHSDA, data discussed above in Section 1, 6.8 million Americans used marijuana weekly in 1998. In addition, the DAWN data discussed in Section 4 indicates that 34.2 % of the 87,150 ED marijuana mentions in 1999 were related to episodes in which the motive for drug intake was primarily dependence. It should be emphasized that the patient-reported "motive" for the drug intake applies to the entire episode and since more than one drug can be mentioned per episode, it may not apply to one specific drug. DAWN data do not distinguish the drug responsible for the ED visit from others used concomitantly. Finally, the CEWG data discussed in Section 4 above reports an increase in the proportion of primary

marijuana users entering drug abuse treatment programs. Thus, there is evidence among a certain proportion of marijuana users for a true psychological dependence syndrome.

8. **WHETHER THE SUBSTANCE IS AN IMMEDIATE PRECURSOR OF A SUBSTANCE ALREADY CONTROLLED UNDER THIS ARTICLE**

Marijuana is not an immediate precursor of another controlled substance.

C. FINDINGS AND RECOMMENDATION

After considering the scientific and medical evidence presented under the eight factors above, FDA finds that marijuana meets the three criteria for placing a substance in Schedule I of the CSA under 21 U.S.C. 812(b)(1). Specifically:

1. Marijuana has a high potential for abuse.

11.2 million Americans used marijuana monthly in 1999 and 1998 data indicate that 6.8 million Americans used marijuana weekly. A 1999 study indicates that by 12th grade, 37.8% of students report having used marijuana in the past year, and 23.1 % report using it monthly. In 1999, 87,150 emergency department episodes were induced by or related to the use of marijuana/ hashish, representing 16% of all drug-related episodes. The primary motive for drug intake in 34.2 % of those episodes was reported to be dependence. DAWN data from that same year show that out of 664 medical examiner episodes involving marijuana, marijuana was the only drug reported in 187 deaths. In recent years, the proportion of primary marijuana abusers entering drug abuse treatment programs has been increasing in major US cities, ranging from 19% in New York City to 41% in St. Louis and Denver.

Data show that humans prefer higher doses of marijuana to lower doses, demonstrating that marijuana has dose-dependent reinforcing effects. Marijuana has relatively low levels of toxicity and physical dependence as compared to other illicit drugs. However, as discussed above, physical dependence and toxicity are not the only factors to consider in determining a substance's abuse potential. The large number of individuals using marijuana on a regular basis and the vast amount of marijuana that is available for illicit use are indicative of widespread use. In addition, there is evidence that marijuana use can result in psychological dependence in a certain proportion of the population.

2. Marijuana has no currently accepted medical use in treatment in the United States.

The FDA has not approved a new drug application for marijuana. The opportunity for scientists to conduct clinical research with marijuana has increased recently due to the implementation of DHHS policy supporting clinical research with botanical marijuana. While there are INDs for marijuana active at the FDA, marijuana does not have a currently accepted medical use for treatment in the United States nor does it have an accepted medical use with severe restrictions.

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.

Alliance for Cannabis Therapeutics v. DEA, 15 F.3d 1131, 1135 (D.C. Cir. 1994).

Although the chemistry of many cannabinoids found in marijuana have been characterized, a complete scientific analysis of all the chemical components found in marijuana has not been conducted. Safety studies for acute or subchronic administration of marijuana have been carried out through a limited number of Phase 1 clinical investigations approved by the FDA, but there have been no studies that have scientifically assessed the efficacy of marijuana for any medical condition. A material conflict of opinion among experts precludes a finding that marijuana has been accepted by qualified experts. At this time, it is clear that there is not a consensus of medical opinion concerning medical applications of marijuana.

Alternately, a drug can be considered to have "a currently accepted medical use with severe restrictions" (21 U.S.C. § 812(b)(2)(B)). Although some evidence exists that some form of marijuana may prove to be effective in treating a number of conditions, research on the medical use of marijuana has not progressed to the point that marijuana can be considered to have a "currently accepted medical use with severe restrictions."

3. **There is a lack of accepted safety for use of marijuana under medical supervision.**

There are no FDA-approved marijuana products. Marijuana does not have a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions. As discussed earlier, the known risks of marijuana use are not outweighed by any potential benefits. In addition, the agency cannot conclude that marijuana has an acceptable level of safety without assurance of a consistent and predictable potency and without proof that the substance is free of contamination. If marijuana is to be investigated more widely for medical use, information and data regarding the chemistry, manufacturing and specifications of marijuana must be developed. Therefore, FDA concludes that, even under medical supervision, marijuana has not been shown to have an acceptable level of safety.

FDA therefore recommends that marijuana be maintained in Schedule I of the CSA.

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