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Debra L. Billingsley, Executive Secretary

Sam Brownback, Governor

**Senate Bill No. 9**
Enacting the Cannabis Compassion and Care Act
Committee on Public Health and Welfare
**Presented by Debra Billingsley**
**On Behalf of**
**The Kansas State Board of Pharmacy**
**January 22, 2015**

Madam Chairperson, Members of the Committee:

My name is Debra Billingsley, and I am the Executive Secretary of the Kansas State Board of Pharmacy. Our Board is created by statute and is comprised of seven members, each of whom is appointed by the Governor. Of the seven, six are licensed pharmacists and one is a member of the general public. They are charged with protecting the health, safety and welfare of the citizens of Kansas and to educate and promote the understanding of pharmacy practices in Kansas.

The Board of Pharmacy wanted to provide information to the committee related to medical marijuana. Currently, marijuana is listed as a schedule I controlled substance federally and in state law (K.S.A. 65-4105). A schedule I drug has a high potential for abuse and has no current accepted medical use in treatment in the United States. There is a lack of accepted safety for use of the drug under medical supervision.

The Department of Justice denied a petition from the Coalition for Rescheduling Cannabis to initiate proceedings to reschedule marijuana federally. The denial was reported in the *Federal Register,* Volume 76, Number 131 (Friday, July 8, 2011). The denial was based on a request to remove marijuana from schedule I and to reschedule cannabis as either a schedule III, IV, or V. The request was based on the following assertions:

1) That cannabis has an accepted medical use in the United States,
2) That cannabis is safe for use under medical supervision,
3) That the potential for abuse is lower than schedule I or II, and
4) That cannabis dependence liability is lower than schedule I or II.

The Drug Enforcement Administration (DEA) requested a scientific medical evaluation and scheduling recommendation from the Department of Health and Human Services (DHHS). I have attached a copy of the information that was provided to the Department of Justice. The Secretary of DHHS is required to consider in a scientific and

medical evaluation eight factors determinative of control under the Controlled Substance Act. Those eight factors are:

1) The actual or relative potential for abuse,
2) Scientific evidence of its pharmacological effects, if known,
3) The state of current scientific knowledge regarding the drug or other substances,
4) Its history and current pattern of abuse,
5) The scope, duration, and significance of abuse,
6) What, if any, risk there is to the public,
7) Its psychic or physiologic dependence liability, and
8) Whether the substance is an immediate precursor of a substance already controlled under this article.

After consideration of the eight factors discussed the DHHS recommended that marijuana remain in schedule I of the Controlled Substance Act. Under state law the Board of Pharmacy is required to determine annually any drugs that should be scheduled, rescheduled or deleted from the Controlled Substance list. Pursuant to K.S.A. 65-4102 the Board must consider the same eight factors when making a recommendation to the legislature. Based on the recommendations of DHHS the Board of Pharmacy would not recommend a change to the Kansas Controlled Substance Act since it would be a hazard to the public safety of the citizens of Kansas.

Thank you for permitting me to provide information.


# FEDERAL REGISTER

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Part IV

## Department of Justice

Drug Enforcement Administration

21 CFR Chapter II

Denial of Petition To Initiate Proceedings To Reschedule Marijuana; Proposed Rule

**DEPARTMENT OF JUSTICE**

**Drug Enforcement Administration**

**21 CFR Chapter II**

**[Docket No. DEA–352N]**

## Denial of Petition To Initiate Proceedings To Reschedule Marijuana

**AGENCY:** Drug Enforcement Administration (DEA), Department of Justice.

**ACTION:** Denial of petition to initiate proceedings to reschedule marijuana.

**SUMMARY:** By letter dated June 21, 2011, the Drug Enforcement Administration (DEA) denied a petition to initiate rulemaking proceedings to reschedule marijuana.[1] Because DEA believes that this matter is of particular interest to members of the public, the agency is publishing below the letter sent to the petitioner (denying the petition), along with the supporting documentation that was attached to the letter.

**FOR FURTHER INFORMATION CONTACT:** Imelda L. Paredes, Office of Diversion Control, Drug Enforcement Administration, 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone (202) 307–7165.

**SUPPLEMENTARY INFORMATION:**

**June 21, 2011.**

Dear Mr. Kennedy:

On October 9, 2002, you petitioned the Drug Enforcement Administration (DEA) to initiate rulemaking proceedings under the rescheduling provisions of the Controlled Substances Act (CSA). Specifically, you petitioned DEA to have marijuana removed from schedule I of the CSA and rescheduled as cannabis in schedule III, IV or V.

You requested that DEA remove marijuana from schedule I based on your assertion that:

(1) Cannabis has an accepted medical use in the United States;

(2) Cannabis is safe for use under medical supervision;

(3) Cannabis has an abuse potential lower than schedule I or II drugs; and

(4) Cannabis has a dependence liability that is lower than schedule I or II drugs.

In accordance with the CSA rescheduling provisions, after gathering the necessary data, DEA requested a scientific and medical evaluation and scheduling recommendation from the Department of Health and Human Services (DHHS). DHHS concluded that marijuana has a high potential for abuse, has no accepted medical use in the United States, and lacks an acceptable level of safety for use even under medical supervision. Therefore, DHHS recommended that marijuana remain in schedule I. The scientific and medical evaluation and scheduling recommendation that DHHS submitted to DEA is attached hereto.

Based on the DHHS evaluation and all other relevant data, DEA has concluded that there is no substantial evidence that marijuana should be removed from schedule I. A document prepared by DEA addressing these materials in detail also is attached hereto. In short, marijuana continues to meet the criteria for schedule I control under the CSA because:

(1) *Marijuana has a high potential for abuse.* The DHHS evaluation and the additional data gathered by DEA show that marijuana has a high potential for abuse.

(2) *Marijuana has no currently accepted medical use in treatment in the United States.* According to established case law, marijuana has no "currently accepted medical use" because: The drug's chemistry is not known and reproducible; there are no adequate safety studies; there are no adequate and well-controlled studies proving efficacy; the drug is not accepted by qualified experts; and the scientific evidence is not widely available.

(3) *Marijuana lacks accepted safety for use under medical supervision.* At present, there are no U.S. Food and Drug Administration (FDA)-approved marijuana products, nor is marijuana under a New Drug Application (NDA) evaluation at the FDA for any indication. Marijuana does not have a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions. At this time, the known risks of marijuana use have not been shown to be outweighed by specific benefits in well-controlled clinical trials that scientifically evaluate safety and efficacy.

You also argued that cannabis has a dependence liability that is lower than schedule I or II drugs. Findings as to the physical or psychological dependence of a drug are only one of eight factors to be considered. As discussed further in the attached documents, DHHS states that long-term, regular use of marijuana can lead to physical dependence and withdrawal following discontinuation as well as psychic addiction or dependence.

The statutory mandate of 21 U.S.C. 812(b) is dispositive. Congress established only one schedule, schedule I, for drugs of abuse with "no currently accepted medical use in treatment in the United States" and "lack of accepted safety for use under medical supervision." 21 U.S.C. 812(b).

Accordingly, and as set forth in detail in the accompanying DHHS and DEA documents, there is no statutory basis under the CSA for DEA to grant your petition to initiate rulemaking proceedings to reschedule marijuana. Your petition is, therefore, hereby denied.

Sincerely,

**Michele M. Leonhart,**

*Administrator.*

Attachments:

Marijuana. Scheduling Review Document: Eight Factor Analysis

Basis for the recommendation for maintaining marijuana in schedule I of the Controlled Substances Act

Date: June 30, 2011

Michele M. Leonhart
*Administrator*

**Department of Health and Human Services,**
Office of the Secretary Assistant Secretary for Health, Office of Public Health and Science Washington, D.C. 20201.

December 6, 2006.

The Honorable Karen P. Tandy
*Administrator, Drug Enforcement Administration, U.S. Department of Justice, Washington, D.C. 20537*

Dear Ms. Tandy:

This is in response to your request of July 2004, 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 of the CSA.

Marijuana is 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 an accepted level of safety for use under medical supervision. Accordingly, HHS recommends that marijuana continue to be subject to control under Schedule I of the CSA. Enclosed is a document prepared by FDA's Controlled Substance Staff that is the basis for this recommendation.

Should you have any questions regarding this recommendation, please contact Corinne P. Moody, of the Controlled Substance Staff, Center for Drug Evaluation and Research. Ms. Moody can be reached at 301–827–1999.

Sincerely yours,
John O. Agwunobi,
*Assistant Secretary for Health.*

Enclosure:

[1] Note that "marihuana" is the spelling originally used in the Controlled Substances Act (CSA). This document uses the spelling that is more common in current usage, "marijuana."

Basis for the Recommendation for Maintaining Marijuana in Schedule I of the Controlled Substances Act

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

On October 9, 2002, the Coalition for Rescheduling Cannabis (hereafter known as the Coalition) submitted a petition to the Drug Enforcement Administration (DEA) requesting that proceedings be initiated to repeal the rules and regulations that place marijuana in Schedule I of the Controlled Substances Act (CSA). The petition contends that cannabis has an accepted medical use in the United States, is safe for use under medical supervision, and has an abuse potential and a dependency liability that is lower than Schedule I or II drugs. The petition requests that marijuana be rescheduled as "cannabis" in either Schedule III, IV, or V of the CSA. In July 2004, the DEA Administrator requested that the Department of Health and Human Services (HHS) provide a scientific and medical evaluation of the available information and a scheduling recommendation for marijuana, in accordance with the provisions of 21 U.S.C. 811(b).

In accordance with 21 U.S.C. 811(b), DEA has gathered information related to the control of marijuana (*Cannabis sativa*)[2] under the CSA. Pursuant to 21 U.S.C. 811(b), the Secretary is required to consider in a scientific and medical evaluation eight factors determinative of control under the CSA. Following consideration of the eight factors, if it is appropriate, the Secretary must make three findings to recommend scheduling a substance in the CSA. The findings relate to a substance's abuse potential, legitimate medical use, and safety or dependence liability.

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).

In this document, FDA recommends the continued control of marijuana in Schedule I of the CSA. Pursuant to 21 U.S.C. 811(c), the eight factors pertaining to the scheduling of marijuana are considered below.

## 1. ITS ACTUAL OR RELATIVE POTENTIAL FOR ABUSE

The first factor the Secretary must consider is marijuana's actual or relative potential for abuse. 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:

a. 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.

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

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.

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 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 tolerance or physical dependence, because drugs may be abused in doses or in patterns that do not induce these phenomena. Animal data, human data, and epidemiological data are all used in determining a substance's abuse liability. Epidemiological data can also be an important indicator of actual abuse. Finally, evidence of clandestine production and illicit trafficking of a substance are also important factors.

**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 abused substance. The pharmacology of the psychoactive constituents of marijuana, including delta$^9$-tetrahydrocannabinol (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 Factor 2, "Scientific Evidence of its Pharmacological Effects, if Known." Data on the extent of marijuana abuse are available from HHS through NIDA and the Substance Abuse and Mental Health Services Administration (SAMHSA). These data are discussed in detail under Factor 4, "Its History and Current Pattern of Abuse;" Factor 5, "The Scope, Duration, and Significance of Abuse;" and Factor 6, "What, if any, Risk There is to the Public Health?"

According to SAMHSA's 2004 National Survey on Drug Use and Health (NSDUH; the database formerly known as the National Household Survey on Drug Abuse (NHSDA)), the latest year for which complete data are available, 14.6 million Americans have used marijuana in the past month. This is an increase of 3.4 million individuals since 1999, when 11.2 million individuals reported using marijuana monthly. (See the discussion of NSDUH data under Factor 4).

The Drug Abuse Warning Network (DAWN), sponsored by SAMHSA, is a national probability survey of U.S. hospitals with emergency departments (EDs) designed to obtain information on ED visits in which recent drug use is implicated; 2003 is the latest year for which complete data are available. Marijuana was involved in 79,663 ED visits (13 percent of drug-related visits). There are a number of risks resulting from both acute and chronic use of marijuana which are discussed in full below under Factors 2 and 6.

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

At present, cannabis is legally available through legitimate channels for research purposes only and thus has a limited potential for diversion. In addition, the lack of significant diversion of investigational supplies may result from the ready availability of illicit cannabis of equal or greater quality. The magnitude of the demand for illicit marijuana is evidenced by DEA/Office of National Drug Control Policy (ONDCP) seizure statistics. Data on marijuana seizures can often highlight trends in the overall trafficking patterns. DEA's Federal-Wide Drug Seizure System (FDSS) provides information on total federal drug seizures. FDSS reports total federal seizures of 2,700,282 pounds of marijuana in 2003, the latest year for which complete data are available (DEA, 2003). This represents nearly a doubling of marijuana seizures since 1995, when 1,381,107 pounds of marijuana were seized by federal agents.

**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.**

[2] 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 there from), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination (21 U.S.C. 802(16)).

The 2004 NSDUH data show that 14.6 million American adults use marijuana on a monthly basis (SAMHSA, 2004), confirming that marijuana has reinforcing properties for many individuals. The FDA has not evaluated or approved a new drug application (NDA) for marijuana for any therapeutic indication, although several investigational new drug (IND) applications are 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 advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.**

The primary psychoactive compound in botanical marijuana is delta$^9$-THC. Other cannabinoids also present in the marijuana plant likely contribute to the psychoactive effects.

There are two drug products containing cannabinoid compounds that are structurally related to the active components in marijuana. Both are controlled under the CSA. Marinol is a Schedule III drug product containing synthetic delta$^9$-THC, known generically as dronabinol, formulated in sesame oil in soft gelatin capsules. Dronabinol is listed in Schedule I. Marinol was approved by the FDA in 1985 for the treatment of two medical conditions: nausea and vomiting associated with cancer chemotherapy in patients that had failed to respond adequately to conventional anti-emetic treatments, and for the treatment of anorexia associated with weight loss in patients with acquired immunodeficiency syndrome or AIDS. Cesamet is a drug product containing the Schedule II substance, nabilone, that was approved for marketing by the FDA in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy. All other structurally related cannabinoids in marijuana are already listed as Schedule I drugs under the CSA.

## 2. SCIENTIFIC EVIDENCE OF ITS PHARMACOLOGICAL EFFECTS, IF KNOWN

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

### Neurochemistry and Pharmacology of Marijuana

Some 483 natural constituents have been identified in marijuana, including approximately 66 compounds that are classified as cannabinoids (Ross and El Sohly, 1995). Cannabinoids are not known to exist in plants other than marijuana, and most of the cannabinoid compounds that occur naturally have been identified chemically. Delta$^9$-THC is considered the major psychoactive cannabinoid constituent of marijuana (Wachtel et al., 2002). The structure and function of delta$^9$-THC was first described in 1964 by Gaoni and Mechoulam.

The site of action of delta$^9$-THC and other cannabinoids was verified with the cloning of cannabinoid receptors, first from rat brain tissue (Matsuda et al., 1990) and then from human brain tissue (Gerard et al., 1991). Two cannabinoid receptors, $CB_1$ and $CB_2$, have subsequently been characterized (Piomelli, 2005).

Autoradiographic studies have provided information on the distribution of cannabinoid receptors. $CB_1$ receptors are found in the basal ganglia, hippocampus, and cerebellum of the brain (Howlett et al., 2004) as well as in the immune system. It is believed that the localization of these receptors may explain cannabinoid interference with movement coordination and effects on memory and cognition. The 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 are found primarily in the immune system, predominantly in B lymphocytes and natural killer cells (Bouaboula et al., 1993). It is believed that the $CB_2$-type receptor is responsible for mediating the immunological effects of cannabinoids (Galiegue et al., 1995).

However, $CB_2$ receptors also have recently been localized in the brain, primarily in the cerebellum and hippocampus (Gong et al., 2006).

The cannabinoid receptors belong to the family of G-protein-coupled receptors and present a typical seven transmembrane-spanning domain structure. Many G-protein-coupled receptors are linked to adenylate cyclase either positively or negatively, depending on the receptor system. Cannabinoid receptors are linked to an inhibitory G-protein (Gi), so that when the receptor is activated, adenylate cyclase activity is inhibited, which prevents the conversion of adenosine triphosphate (ATP)to the second messenger cyclic adenosine monophosphate (cAMP). Examples of inhibitory-coupled receptors include: opioid, muscarinic cholinergic, alpha $_2$-adrenoreceptors, dopamine ($D_2$), and serotonin ($5\text{-}HT_1$).

It has been shown that $CB_1$, but not $CB_2$ receptors, inhibit N- and P/Q type calcium channels and activate inwardly rectifying potassium channels (Mackie et al., 1995; Twitchell et al., 1997). Inhibition of the N-type calcium channels decreases neurotransmitter release from several tissues and this may be the mechanism by which cannabinoids inhibit acetylcholine, norepinephrine, 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). When cannabinoids are given subacutely to rats, there is a down-regulation of $CB_1$ receptors, as well as a decrease in GTPgammaS binding, the second messenger system coupled to $CB_1$ receptors (Breivogel et al., 2001).

Delta$^9$-THC displays similar affinity for $CB_1$ and $CB_2$ receptors but behaves as a weak agonist for $CB_2$ receptors, based on inhibition of adenylate cyclase. The identification of synthetic cannabinoid ligands that selectively bind to $CB_2$ receptors but do not have the typical delta$^9$-THC-like psychoactive properties suggests that the psychotropic effects of cannabinoids are mediated through the activation of $CB_1$-receptors (Hanus et al., 1999). Naturally-occurring cannabinoid agonists, such as delta$^9$-THC, and the synthetic cannabinoid agonists such as WIN–55,212–2 and CP–55,940 produce hypothermia, analgesia, hypoactivity, and cataplexy in addition to their psychoactive effects.

In 2000, two endogenous cannabinoid receptor agonists, anandamide and arachidonyl glycerol (2–AG), were discovered. Anandamide is a low efficacy agonist (Breivogel and Childers, 2000), 2–AG is a highly efficacious agonist (Gonsiorek et al., 2000). Cannabinoid endogenous ligands are present in central as well as peripheral tissues. The action of the endogenous ligands is terminated by a combination of uptake and hydrolysis. The physiological role of endogenous cannabinoids is an active area of research (Martin et al., 1999).

Progress in cannabinoid pharmacology, including further characterization of the cannabinoid receptors, isolation of endogenous cannabinoid ligands, synthesis of agonists and antagonists with variable affinity, and selectivity for cannabinoid receptors, provide the foundation for the potential elucidation of cannabinoid-mediated effects and their relationship to psychomotor disorders, memory, cognitive functions, analgesia, anti-emesis, intraocular and systemic blood pressure modulation, bronchodilation, and inflammation.

### Central Nervous System Effects

*Human Physiological and Psychological Effects*

Subjective Effects

The physiological, psychological, and behavioral effects of marijuana vary among individuals. Common responses to cannabinoids, as described by Adams and Martin (1996) and others (Hollister, 1986 and 1988; Institute of Medicine, 1982) are listed below:

1) Dizziness, nausea, tachycardia, facial flushing, dry mouth, and tremor 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, especially at high doses

8) Impaired judgment, 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, especially in inexperienced users or in those who have taken a large dose

10) Increased appetite and short-term memory impairment

These subjective responses to marijuana are pleasurable to many humans and are associated with drug-seeking and drug-taking (Maldonado, 2002).

The short-term perceptual distortions and psychological alterations produced by marijuana have been characterized by some researchers as acute or transient psychosis (Favrat et al., 2005). However, the full response to cannabinoids is dissimilar to the DSM–IV–TR criteria for a diagnosis of one of the psychotic disorders (DSM–IV–TR, 2000).

As with many psychoactive drugs, an individual's response to marijuana can be influenced by that person's medical/psychiatric history and history with drugs. 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). Dose preferences have been demonstrated for marijuana in which higher doses (1.95 percent delta$^9$-THC) are preferred over lower doses (0.63 percent delta$^9$-THC) (Chait and Burke, 1994).

Behavioral Impairment

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 to human volunteers of 290 micrograms per kilogram (µg/kg) delta$^9$-THC in a smoked marijuana cigarette resulted in impaired perceptual motor speed and accuracy, two skills that are critical to driving ability (Kurzthaler et al., 1999). Similarly, administration of 3.95 percent delta$^9$-THC in a smoked marijuana cigarette increased disequilibrium 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 fully resolve until at least 1 day after the acute psychoactive effects have subsided, following repeated administration. Heishman et al. (1990) showed that impairment on memory tasks persists for 24 hours after smoking marijuana cigarettes containing 2.57 percent delta$^9$-THC. However, Fant et al. (1998) showed minimal residual alterations in subjective or performance measures the day after subjects were exposed to 1.8 percent or 3.6 percent smoked delta$^9$-THC.

The effects of chronic marijuana use have also been investigated. Marijuana did not appear to have residual effects on performance of a comprehensive neuropsychological battery when 54 monozygotic male twins (one of whom used marijuana, one of whom did not) were compared 1–20 years after cessation of marijuana use (Lyons et al., 2004). This conclusion is similar to the results from an earlier study of marijuana's effects on cognition in 1,318 participants over a 15-year period, where there was no evidence of long-term residual effects (Lyketsos et al., 1999). In contrast, Solowij et al. (2002) demonstrated that 51 long-term cannabis users did less well than 33 non-using controls or 51 short-term users on certain tasks of memory and attention, but users in this study were abstinent for only 17 hours at time of testing. A recent study noted that heavy, frequent cannabis users, abstinent for at least 24 hours, performed significantly worse than controls on verbal memory and psychomotor speed tests (Messinis et al, 2006).

Pope et al. (2003) reported that no differences were seen in neuropsychological performance in early- or late-onset users compared to non-using controls, after adjustment for intelligence quotient (IQ). In another cohort of chronic, heavy marijuana users, some deficits were observed on memory tests up to a week following supervised abstinence, but these effects disappeared by day 28 of abstinence (Harrison et al., 2002). The authors concluded that, "cannabis-associated cognitive deficits are reversible and related to recent cannabis exposure, rather than irreversible and related to cumulative lifetime use." Other investigators have reported neuropsychological deficits in memory, executive functioning, psychomotor speed, and manual dexterity in heavy marijuana smokers who had been abstinent for 28 days (Bolla et al., 2002). A follow up study of heavy marijuana users noted decision-making deficits after 25 days of abstinence (Bolla et al., 2005). Finally, when IQ was contrasted in adolescents at 9–12 years and at 17–20 years, current heavy marijuana users showed a 4-point reduction in IQ in later adolescence compared to those who did not use marijuana (Fried et al., 2002).

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 age 16 (Ehrenreich et al., 1999). Kandel and Chen (2000) assert that 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.

Heavy marijuana users were contrasted with an age matched control group in a case-control design. The heavy users reported lower educational achievement and lower income than controls, a difference that persisted after confounding variables were taken into account. Additionally, the users also reported negative effects of marijuana use on cognition, memory, career, social life, and physical and mental health (Gruber et al., 2003).

Association with Psychosis

Extensive research has been conducted recently to investigate whether exposure to marijuana is associated with schizophrenia or other psychoses. While many studies are small and inferential, other studies in the literature utilize hundreds to thousands of subjects.

At present, the data do not suggest a causative link between marijuana use and the development of psychosis. Although some individuals who use marijuana have received a diagnosis of psychosis, most reports conclude that prodromal symptoms of schizophrenia appear prior to marijuana use (Schiffman et al., 2005). When psychiatric symptoms are assessed in individuals with chronic psychosis, the "schizophrenic cluster" of symptoms is significantly observed among individuals who do not have a history of marijuana use, while "mood cluster" symptoms are significantly observed in individuals who do have a history of marijuana use (Maremmani et al., 2004).

In the largest study evaluating the link between psychosis and drug use, 3 percent of 50,000 Swedish conscripts who used marijuana more than 50 times went on to develop schizophrenia (Andreasson et al., 1987). This was interpreted by the authors to suggest that marijuana use increased the risk for the disorder only among those individuals who were predisposed to develop psychosis. A similar conclusion was drawn when the prevalence of schizophrenia was modeled against marijuana use across birth cohorts in Australia between the years 1940 to 1979 (Degenhardt et al., 2003). Although marijuana use increased over time in adults born during the 4-decade period, there was not a corresponding increase in diagnoses for psychosis in these individuals. The authors conclude that marijuana may precipitate schizophrenic disorders only in those individuals who are vulnerable to developing psychosis. Thus, marijuana per se does not appear to induce schizophrenia in the majority of individuals who try or continue to use the drug.

However, as might be expected, the acute intoxication produced by marijuana does exacerbate the perceptual and cognitive deficits of psychosis in individuals who have been previously diagnosed with the condition (Schiffman et al., 2005; Hall et al., 2004; Mathers and Ghodse, 1992; Thornicroft, 1990). This is consistent with a 25-year longitudinal study of over 1,000 individuals who had a higher rate of experiencing some symptoms of psychosis (but who did not receive a diagnosis of psychosis) if they were daily marijuana users than if they were not (Fergusson et al., 2005). A shorter, 3-year longitudinal study with over 4,000 subjects similarly showed that psychotic symptoms, but not diagnoses, were more prevalent in subjects who used marijuana (van Os et al., 2002).

Additionally, schizophrenic individuals stabilized with antipsychotics do not respond differently to marijuana than healthy controls (D'Souza et al., 2005), suggesting that psychosis and/or antipsychotics do not biochemically alter cannabinoid systems in the brain.

Interestingly, cannabis use prior to a first psychotic episode appeared to spare neurocognitive deficits compared to patients who had not used marijuana (Stirling et al., 2005). Although adolescents diagnosed with a first psychotic episode used more marijuana than adults who had their first psychotic break, adolescents and adults had similar clinical outcomes 2 years later (Pencer et al., 2005).

Heavy marijuana users, though, do not perform differently than non-users on the Stroop task, a classic psychometric instrument that measures executive cognitive functioning. Since psychotic individuals do not perform the Stroop task well, alterations in executive functioning consistent with a psychotic profile were not apparent following chronic exposure to marijuana (Gruber and Yurgelun-Todd, 2005; Eldreth et al., 2004).

Alteration in Brain Structure

Although evidence suggests that some drugs of abuse can lead to changes in the density or structure of the brain in humans, there are currently no data showing that exposure to marijuana can induce such alterations. A recent comparison of long-term marijuana smokers to non-smoking control subjects using magnetic resonance imaging (MRI) did not reveal any differences in the volume of grey or white matter, in the hippocampus, or in cerebrospinal fluid volume, between the two groups (Tzilos et al., 2005).

Behavioral Effects of Prenatal Exposure

The impact of in utero marijuana exposure on performance in a series of cognitive tasks has been studied in children at different stages of development. However, since many marijuana users have abused other drugs, it is difficult to determine the specific impact of marijuana on prenatal exposure.

Differences in several cognitive domains distinguished the 4-year-old children of heavy marijuana users. In particular, memory and verbal measures are negatively associated with maternal marijuana use (Fried and Watkinson, 1987). Maternal marijuana use is predictive of poorer performance on abstract/visual reasoning tasks, although it is not associated with an overall lowered IQ in 3-year old children (Griffith et al., 1994). At 6 years of age, prenatal marijuana history is associated with an increase in omission errors on a vigilance task, possibly reflecting a deficit in sustained attention (Fried et al., 1992). When the effect of prenatal exposure in 9–12 year old children is analyzed, in utero marijuana exposure is negatively associated with executive function tasks that require impulse control, visual analysis, and hypothesis testing, and it is not associated with global intelligence (Fried et al., 1998).

Marijuana as a "Gateway Drug"

The Institute of Medicine (IOM) reported that the widely held belief that marijuana is a "gateway drug," leading to subsequent abuse of other illicit drugs, lacks conclusive evidence (Institute of Medicine, 1999). Recently, Fergusson et al. (2005) in a 25-year study of 1,256 New Zealand children concluded that use of marijuana correlates to an increased risk of abuse of other drugs, including cocaine and heroin. Other sources, however, do not support a direct causal relationship between regular marijuana and other illicit drug use. In general, such studies are selective in recruiting individuals who, in addition to having extensive histories of marijuana use, are influenced by myriad social, biological, and economic factors that contribute to extensive drug abuse (Hall and Lynskey, 2005). For most studies that test the hypothesis that marijuana causes abuse of harder drugs, the determinative measure of choice is any drug use, rather than DSM–IV–TR criteria for drug abuse or dependence (DSM–IV–TR, 2000).

According to Golub & Johnson (2001), the rate of progression to hard drug use by youth born in the 1970's, as opposed to youth born between World War II and the 1960's, is significantly decreased, although overall marijuana use among youth appears to be increasing. Nace et al. (1975) reported that even in the Vietnam-era soldiers who extensively abused marijuana and heroin, there was a lack of correlation of a causal relationship demonstrating marijuana use leading to heroin addiction. A recent longitudinal study of 708 adolescents demonstrated that early onset marijuana use did not lead to problematic drug use (Kandel and Chen, 2000). Similarly, among 2,446 adolescents followed longitudinally, cannabis dependence was uncommon but when it did occur, it was predicted primarily by parental death, deprived socio-economic status, and baseline use of illicit drugs other than marijuana (von Sydow et al., 2002).

*Animal behavioral effects*

Self-Administration

Self-administration is a method that assesses whether a drug produces rewarding effects that increase the likelihood of behavioral responses in order to obtain additional drug. Drugs that are self-administered by animals are likely to produce rewarding effects in humans, which is indicative of abuse liability. Generally, a good correlation exists between those drugs that are self-administered by rhesus monkeys and those that are abused by humans (Balster and Bigelow, 2003).

Interestingly, self-administration of hallucinogenic-like drugs, such as cannabinoids, lysergic acid diethylamide (LSD), and mescaline, has been difficult to demonstrate in animals (Yanagita, 1980). However, when it is known that humans voluntarily consume a particular drug (such as cannabis) for its pleasurable effects, the inability to establish self-administration with that drug in animals has no practical importance in the assessment of abuse potential. This is because the animal test is a predictor of human behavioral response in the absence of naturalistic data.

The experimental literature generally reports that naïve animals will not self-administer cannabinoids unless they have had previous experience with other drugs of abuse. However, when squirrel monkeys are first trained to self-administer intravenous cocaine, they will continue to bar-press at the same rate as when delta$^9$-THC is substituted for cocaine, at doses that are comparable to those used by humans who smoke marijuana (Tanda et al., 2000). This effect is blocked by the cannabinoid receptor antagonist, SR 141716. New studies show that monkeys without a history of any drug exposure can be successfully trained to self-administer delta$^9$-THC intravenously (Justinova et al., 2003). The maximal rate of responding is 4 µg/kg/injection, which is 2–3 times greater than that observed in previous studies using cocaine-experienced monkeys.

These data demonstrate that under specific pretreatment conditions, an animal model of reinforcement by cannabinoids now exists for future investigations. Rats will self-administer delta$^9$-THC when it is applied intracerebroventricularly (i.c.v.), but only at the lowest doses tested (0.01–0.02 µg/infusion) (Braida et al., 2004). This effect is antagonized by the cannabinoid antagonist SR141716 and by the opioid antagonist naloxone (Braida et al., 2004). Additionally, mice will 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 that received high doses of WIN 55212 (Chaperon et al., 1998) or delta$^9$-THC (Sanudo-Pena et al., 1997). SR 141716 reversed these aversive effects in both studies.

Conditioned Place Preference

Conditioned place preference (CPP) is a less rigorous method than self-administration of determining whether drugs have rewarding properties. In this behavioral test, animals are given the opportunity to spend time in two distinct environments: one where they previously received a drug and one where they received a placebo. If the drug is reinforcing, animals will choose to spend more time in the environment paired with the drug than the one paired with the placebo, when both options are presented simultaneously.

Animals show CPP to delta$^9$-THC, but only at the lowest doses tested (0.075–0.75 mg/kg, i.p.) (Braida et al., 2004). This effect is antagonized by the cannabinoid antagonist, SR141716, as well as by the opioid antagonist, naloxone (Braida et al., 2004). However, SR141716 may be a partial agonist, rather than a full antagonist, since it is also able to induce CPP (Cheer et al., 2000). Interestingly, in knockout mice, animals without µ-opioid receptors do not develop CPP to delta$^9$-THC (Ghozland et al., 2002).

Drug Discrimination Studies

Drug discrimination is a method in which animals indicate whether a test drug produces physical or psychic perceptions similar to those produced by a known drug of abuse. In this test, an animal learns to press one bar when it receives the known drug of abuse and another bar when it receives placebo. A challenge session with the test drug determines which of the two

bars the animal presses more often, as an indicator of whether the test drug is like the known drug of abuse.

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; Barnett et al., 1985; Browne and Weissman, 1981; Wiley et al., 1993; Wiley et al., 1995). Additionally, the major active metabolite of delta$^9$-THC, 11-hydroxy-delta$^9$-THC, also generalizes to the stimulus cue elicited by delta$^9$-THC (Browne and Weissman, 1981). Twenty-two other cannabinoids found in marijuana also fully substitute 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 do not fully substitute for delta$^9$-THC.

**Tolerance and Physical Dependence**

Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time (American Academy of Pain Medicine, American Pain Society and American Society of Addiction Medicine consensus document, 2001). Physical dependence is a state of adaptation manifested by a drug class-specific withdrawal syndrome produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist (*ibid*).

The presence of tolerance or physical dependence does not determine whether a drug has abuse potential, in the absence of other abuse indicators such as rewarding properties. Many medications that are not associated with abuse or addiction, such as antidepressants, beta-blockers, and centrally acting antihypertensive drugs, can produce physical dependence and withdrawal symptoms after chronic use.

Tolerance to the subjective and performance effects of marijuana has not been demonstrated in studies with humans. For example, reaction times are not altered by acute administration of marijuana in long term marijuana users (Block and Wittenborn, 1985). This may be related to recent electrophysiological data showing that the ability of delta$^9$-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, and sleep alterations (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; Oviedo et al., 1993).

Acute administration of marijuana containing 2.1 percent delta$^9$-THC does not produce "hangover effects" (Chait et al., 1985). In chronic marijuana users, though, a marijuana withdrawal syndrome has been described that consists of restlessness, irritability, mild agitation, insomnia, sleep EEG disturbances, nausea, and cramping that resolves within a few days (Haney et al., 1999). However, the American Psychiatric Association's Diagnostic and Statistical Manual (DSM–IV–TR, 2000) does not include a listing for cannabis withdrawal syndrome because, "symptoms of cannabis withdrawal . . . have been described . . . but their clinical significance is uncertain." A review of all current clinical studies on cannabis withdrawal led to the recommendation by Budney et al. (2004) that the DSM introduce a listing for cannabis withdrawal that includes such symptoms as sleep difficulties, strange dreams, decreased appetite, decreased weight, anger, irritability, and anxiety. Based on clinical descriptions, this syndrome appears to be mild compared to classical alcohol and barbiturate withdrawal syndromes, which can include more serious symptoms such as agitation, paranoia, and seizures. A recent study comparing marijuana and tobacco withdrawal symptoms in humans demonstrated that the magnitude and timecourse of the two withdrawal syndromes are similar (Vandrey et al., 2005).

The production of an overt withdrawal syndrome in animals following chronic delta$^9$-THC administration has been variably demonstrated under conditions of natural discontinuation. This may be the result of the slow release of cannabinoids from adipose storage, as well as the presence of the major psychoactive metabolite, 11-hydroxy-delta$^9$-THC. When investigators have shown such a withdrawal syndrome in monkeys following the termination of cannabinoid administration, the behaviors included transient aggression, anorexia, biting, irritability, scratching, and yawning (Budney et al., 2004). However, in rodents treated with a cannabinoid antagonist following subacute administration of delta$^9$-THC, pronounced withdrawal symptoms, including wet dog shakes, can be provoked (Breivogel et al., 2003).

**Behavioral Sensitization**

Sensitization to the effects of drugs is the opposite of tolerance: instead of a reduction in behavioral response upon repeated drug administration, animals that are sensitized demonstrate an increase in behavioral response. Cadoni et al. (2001) demonstrated that repeated exposure to delta$^9$-THC can induce sensitization to a variety of cannabinoids. These same animals also have a sensitized response to administration of opioids, an effect known as cross-sensitization. Conversely, when animals were sensitized to the effects of morphine, there was cross-sensitization to cannabinoids. Thus, the cannabinoid and opioids systems appear to operate symmetrically in terms of cross-sensitization.

**Cardiovascular and Autonomic Effects**

Single smoked or oral doses of delta$^9$-THC produce tachycardia and may increase 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 endocannabinoids have been shown to elicit hypotension and bradycardia via activation of peripherally-located $CB_1$ receptors (Wagner et al., 1998). This study suggests that the mechanism of this effect is through presynaptic $CB_1$ receptor-mediated inhibition of norepinephrine release from peripheral sympathetic nerve terminals, with possible additional direct vasodilation via activation of vascular cannabinoid receptors.

The impaired circulatory responses following delta$^9$-THC administration to standing, exercise, Valsalva maneuver, and cold pressor testing suggest that cannabinoids induce a state of sympathetic insufficiency. In humans, tolerance can develop to the orthostatic hypotension (Jones, 2002; Sidney, 2002), possibly related to plasma volume expansion, but does not develop to the supine hypotensive effects (Benowitz and Jones, 1975). During chronic marijuana ingestion, nearly complete tolerance develops to tachycardia and psychological effects when subjects are challenged with smoked marijuana. Electrocardiographic changes are minimal even after large cumulative doses of delta$^9$-THC. (Benowitz and Jones, 1975).

It is notable that marijuana smoking by older patients, particularly those with some degree of coronary artery or cerebrovascular disease, poses risks related to increased cardiac work, increased catecholamines, carboxyhemoglobin, and postural hypotension (Benowitz and Jones, 1981; Hollister, 1988).

**Respiratory Effects**

Transient bronchodilation is the most typical effect following acute exposure to marijuana (Gong et al., 1984). Long-term use of marijuana can lead to an increased frequency of chronic bronchitis and pharyngitis, as well as chronic cough and increased sputum. Pulmonary function tests reveal that large-airway obstruction can occur with chronic marijuana smoking, as can cellular inflammatory histopathological abnormalities in bronchial epithelium (Adams and Martin, 1996; Hollister, 1986).

The evidence that marijuana may lead to cancer associated with respiratory effects is inconsistent, with some studies suggesting a positive correlation while others do not (Tashkin, 2005). Several cases of lung cancer have been reported in young marijuana users with no history of tobacco smoking or other significant risk factors (Fung et al., 1999). Marijuana use may dose-dependently interact with mutagenic sensitivity, cigarette smoking and alcohol use to increase the risk of head and neck cancer (Zhang et al., 1999). However, in the largest study to date with 1,650 subjects, no positive association was found between marijuana use and lung cancer (Tashkin et al., 2006). This finding held true regardless of extent of marijuana use, when tobacco use and other potential confounding factors were controlled.

The lack of evidence for carcinogenicity related to cannabis may be related to the fact that intoxication from marijuana does not require large amounts of smoked material.

This may be especially pertinent since marijuana is reportedly more potent today than a generation ago. Thus, individuals may consume much less marijuana than in previous decades to reach the desired subjective effects, exposing them to less potential carcinogens.

**Endocrine System**

The presence of in vitro delta$^9$-THC reduces binding of the corticosteroid, dexamethasone, in hippocampal tissue from adrenalectomized rats, suggesting an interaction with the glucocorticoid receptor (Eldridge et al., 1991). Acute delta$^9$-THC releases corticosterone, but tolerance develops to this effect with chronic administration (Eldridge et al., 1991).

Experimental administration of marijuana to humans does not consistently alter endocrine parameters. In an early study, male subjects who experimentally received smoked marijuana showed a significant depression in luteinizing hormone and a significant increase in cortisol were observed (Cone et al., 1986). However, two later studies showed no changes in hormones. Male subjects who were experimentally exposed to smoked delta$^9$-THC (18 mg/marijuana cigarette) or oral delta$^9$-THC (10 mg t.i.d. for 3 days and on the morning of the fourth day) showed no changes in plasma prolactin, ACTH, cortisol, luteinizing hormone, or testosterone levels (Dax et al., 1989). Similarly, a study with 93 men and 56 women showed that chronic marijuana use did not significantly alter concentrations of testosterone, luteinizing hormone, follicle stimulating hormone, prolactin, or cortisol (Block et al., 1991).

Relatively little research has been performed on the effects of experimentally administered marijuana on female reproductive system functioning. In monkeys, delta$^9$-THC administration suppressed ovulation (Asch et al., 1981) and reduced progesterone levels (Almirez et al., 1983). However, when women were studied following experimental exposure to smoked marijuana, no hormonal or menstrual cycle changes were observed (Mendelson and Mello, 1984). Brown and Dobs (2002) suggest that the discrepancy between animal and human hormonal response to cannabinoids may be attributed to the development of tolerance in humans.

Recent data suggest that cannabinoid agonists may have therapeutic value in the treatment of prostate cancer, a type of carcinoma in which growth is stimulated by androgens. Research with prostate cancer cells shows that the mixed $CB_1/CB_2$ agonist, WIN–55212–2, induces apoptosis in prostate cancer cell growth, as well as decreases in expression of androgen receptors and prostate-specific antigens (Sarfaraz et al., 2005).

**Immune System**

Immune functions are altered by cannabinoids, but there can be differences between the effects of synthetic, natural, and endogenous cannabinoids, often in an apparently biphasic manner depending on dose (Croxford and Yamamura, 2005).

Abrams et al. (2003) investigated the effect of marijuana on immunological functioning in 62 AIDS patients who were taking protease inhibitors. Subjects received one of the following three times a day: smoked marijuana cigarette containing 3.95 percent delta$^9$-THC; oral tablet containing delta$^9$-THC (2.5 mg oral dronabinol); or oral placebo. There were no changes in CD4+ and CD8+ cell counts or HIV RNA levels or protease inhibitor levels between groups, demonstrating no short-term adverse virologic effects from using cannabinoids in individuals with compromised immune systems.

These human data contrast with data generated in immunodeficient mice showing that exposure to delta$^9$-THC in vivo suppresses immune function, increases HIV co-receptor expression, and acts as a cofactor to enhance HIV replication (Roth et al., 2005).

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

The third factor the Secretary must consider is the state of current scientific knowledge regarding marijuana. Thus, this section discusses the chemistry, human pharmacokinetics, and medical uses of marijuana.

**Chemistry**

According to the DEA, Cannabis sativa is the primary species of cannabis currently marketed illegally in the United States of America. From this plant, three derivatives are sold as separate illicit drug products: marijuana, hashish, and hashish oil.

Each of these derivatives contains a complex mixture of chemicals. Among the components are the 21 carbon terpenes found in the plant as well as their carboxylic acids, analogues, and transformation products known as cannabinoids (Agurell et al., 1984 and 1986; Mechoulam, 1973). The cannabinoids appear to naturally occur only in the marijuana plant and most of the botanically-derived cannabinoids have been identified. Among the cannabinoids, delta$^9$-THC (alternate name delta$^1$-THC) and delta-8-tetrahydrocannabinol (delta$^8$-THC, alternate name delta$^6$-THC) are both found in marijuana and are able to produce the characteristic 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. Delta$^8$-THC is found only in few varieties of the plant (Hively et al., 1966).

Delta$^9$-THC is an optically active resinous substance, insoluble in water, and extremely lipid soluble. Chemically delta$^9$-THC is (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 (-)-trans isomer of delta$^9$-THC is pharmacologically 6 to 100 times more potent than the (+)-trans isomer (Dewey et al., 1984).

Other cannabinoids, such as cannabidiol (CBD) and cannabinol (CBN), have 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 and 1986; Hollister, 1986).

Marijuana is a mixture of the dried flowering tops and leaves from the plant and is variable in content and potency (Agurell et al., 1984 and 1986; Graham, 1976; Mechoulam, 1973). Marijuana is usually smoked in the form of rolled cigarettes while hashish and hash oil are smoked in pipes. Potency of marijuana, as indicated by cannabinoid content, has been reported to average from as low as 1 to 2 percent to as high as 17 percent.

The concentration of delta$^9$-THC and other cannabinoids in marijuana varies with growing conditions and processing after harvest. Other variables that can influence the strength, quality, and purity of marijuana are genetic differences among the cannabis plant species and which parts of the plant are collected (flowers, leaves, stems, etc.) (Adams and Martin, 1996; Agurell et al., 1984; Mechoulam, 1973). In the usual mixture of leaves and stems distributed as marijuana, the concentration of delta$^9$-THC ranges widely from 0.3 to 4.0 percent by weight. However, specially grown and selected marijuana can contain even 15 percent or greater delta$^9$-THC. Thus, a 1 gm marijuana cigarette might contain as little as 3 mg or as much as 150 mg or more of delta$^9$-THC.

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 a pipe and smoked. DEA reports that cannabinoid content in hashish averages 6 percent.

Hash oil is produced by solvent extraction of the cannabinoids from plant material. 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 (DEA, 2005).

The lack of a consistent concentration of delta$^9$-THC in botanical marijuana from diverse sources complicates the interpretation of clinical data using marijuana. 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.

**Human Pharmacokinetics**

Marijuana is generally smoked as a cigarette (weighing between 0.5 and 1.0 gm), or in a pipe. It can also be taken orally in foods or as extracts of plant material in ethanol or other solvents.

The absorption, metabolism, and pharmacokinetic profile of delta$^9$-THC (and other cannabinoids) in marijuana or other drug products containing delta$^9$-THC vary with route of administration and formulation (Adams and Martin, 1996; Agurell et al., 1984 and 1986). When marijuana is administered by smoking, delta$^9$-THC in the form of an aerosol is absorbed within seconds. The psychoactive effects of marijuana occur immediately following absorption, with mental and behavioral effects measurable up to 6 hours (Grotenhermen, 2003; Hollister,

1986 and 1988). Delta$^9$-THC is delivered to the brain rapidly and efficiently as would be expected of a very lipid-soluble drug.

The bioavailability of the delta$^9$-THC from marijuana in a cigarette or pipe can range from 1 to 24 percent with the fraction absorbed rarely exceeding 10 to 20 percent (Agurell et al., 1986; Hollister, 1988). The relatively low and variable bioavailability results from the following: significant loss of delta$^9$-THC in side-stream smoke, variation in individual smoking behaviors, cannabinoid pyrolysis, incomplete absorption of inhaled smoke, and metabolism in the lungs. A individual's experience and technique with smoking marijuana is an important determinant of the dose that is absorbed (Herning et al., 1986; Johansson et al., 1989).

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 and 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 and 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 (Hunt and Jones, 1980), though reported estimates vary as expected with any slowly cleared substance and the use of assays of variable sensitivities. Lemberger et al. (1970) determined the half-life of delta$^9$-THC to range from 23 to 28 hours in heavy marijuana users to 60 to 70 hours in naïve users.

Characterization of the pharmacokinetics of delta$^9$-THC and other cannabinoids from smoked marijuana is difficult (Agurell et al., 1986; Herning et al., 1986; Huestis et al., 1992a), in part because a subject's smoking behavior during an experiment is variable. Each puff delivers a discrete dose of delta$^9$-THC. 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. For example, under naturalistic conditions, users will hold marijuana smoke in the lungs for an extended period of time, in order to prolong absorption and increase psychoactive effects. The effect of experience in the psychological response may explain why venous blood levels of delta$^9$-THC correlate poorly with intensity of effects and level of intoxication (Agurell et al., 1986; Barnett et al., 1985; Huestis et al., 1992a).

Additionally, 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.

In contrast to smoking, the onset of effects after oral administration of delta$^9$-THC or marijuana is 30 to 90 min, which peaks after 2 to 3 hours and continues for 4 to 12 hours (Grotenhermen, 2003; Adams and Martin, 1996; Agurell et al., 1984 and 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 and 1986). Following oral administration of radioactive-labeled delta$^9$-THC, delta$^9$-THC plasma levels are low relative to those levels after smoking or intravenous administration. There is inter- and intra-subject variability, even when repeated dosing occurs under controlled 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. It is more difficult for a user to titrate the oral delta$^9$-THC dose than marijuana smoking because of the delay in onset of effects after an oral dose (typically 1 to 2 hours).

Cannabinoid metabolism is extensive. Delta$^9$-THC is metabolized via microsomal hydroxylation to both active and inactive metabolites (Lemberger et al., 1970, 1972a, and 1972b; Agurell et al., 1986; Hollister, 1988) of which the primary active metabolite was 11-hydroxy-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). After oral administration, metabolite levels may exceed that of delta$^9$-THC and thus contribute greatly to the pharmacological effects of oral delta$^9$-THC or marijuana. In addition to 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. The majority 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).

### Medical Uses for Marijuana

A NDA for marijuana/cannabis has not been submitted to the FDA for any indication and thus no medicinal product containing botanical cannabis has been approved for marketing. However, small clinical studies published in the current medical literature demonstrate that research with marijuana is being conducted in humans in the United States under FDA-authorized investigational new drug (IND) applications.

HHS states in a published guidance that it is committed to providing "research-grade marijuana for studies that are the most likely to yield usable, essential data" (HHS, 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 NIDA, the only legitimate source of the drug for research in the United States. In May 1999, HHS 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 whether cannabinoids have medical use through scientifically valid investigations.

In February 1997, a National Institutes of Health (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 supported the 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 individuals 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.

For example, in 2000, the state of California established the Center for Medicinal Cannabis Research (CMCR) (*www.cmcr.ucsd.edu*) "in response to scientific evidence for therapeutic possibilities of cannabis and local legislative initiatives in favor of compassionate use" (Grant, 2005). State legislation establishing the CMCR called for high quality medical research that will "enhance understanding of the efficacy and adverse effects of marijuana as a pharmacological agent," but stressed that the project "should not be construed as encouraging or sanctioning the social or recreational use of marijuana." CMCR has thus far funded studies on the potential use of cannabinoids for the treatment of multiple sclerosis, neuropathic pain, appetite suppression and cachexia, and severe pain and nausea related to cancer or its treatment by chemotherapy. To date, though, no NDAs utilizing marijuana for these indications have been submitted to the FDA.

However, FDA approval of an NDA is not the sole means through which a drug can be determined to have a "currently accepted medical use" under the CSA. According to established case law, 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 structures 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 NDA-quality studies that have scientifically assessed the efficacy and full safety profile 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. Finally, the scientific evidence regarding the safety or efficacy of marijuana is typically available only in summarized form, such as in a paper published in the medical literature, rather than in a raw data format. As such, there is no opportunity for adequate scientific scrutiny of whether the data demonstrate safety or efficacy.

Alternately, a drug can be considered to have "a currently accepted medical use with severe restrictions" (21 U.S.C. 812(b)(2)(B)), as allowed under the stipulations for a Schedule II drug. However, as stated above, a material conflict of opinion among experts precludes a finding that marijuana has been accepted by qualified experts, even under conditions where its use is severely restricted. Thus, to date, 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" or a "currently accepted medical use with severe restrictions."

**4. ITS HISTORY AND CURRENT PATTERN OF ABUSE**

The fourth factor the Secretary must consider is the history and current pattern of abuse of marijuana. A variety of sources provide data necessary to assess abuse patterns and trends of marijuana. The data indicators of marijuana use include NSDUH, Monitoring the Future (MTF), DAWN, and Treatment Episode Data Set (TEDS), which are described below:

**National Survey on Drug Use and Health**

The National Survey on Drug Use and Health (NSDUH, 2004; *http://oas.samhsa.gov/nsduh.htm*) is conducted annually by SAMHSA, an agency of HHS. NSDUH provides estimates of the prevalence and incidence of illicit drug, alcohol, and tobacco use in the United States. This database was known until 2001 as the National Household Survey on Drug Abuse. The survey is based on a nationally representative sample of the civilian, non-institutionalized population 12 years of age and older. The survey identifies whether an individual used a drug during a certain period, but not the amount of the drug used on each occasion. Excluded groups include homeless people, active military personnel, and residents of institutions, such as jails.

According to the 2004 NSDUH, 19.1 million individuals (7.9 percent of the U.S. population) illicitly used drugs other than alcohol and nicotine on a monthly basis, compared to 14.8 million (6.7 percent of the U.S. population) users in 1999. This is an increase from 1999 of 4.3 million (2.0 percent of the U.S. population). The most frequently used illicit drug was marijuana, with 14.6 million individuals (6.1 percent of the U.S. population) using it monthly. Thus, regular illicit drug use, and more specifically marijuana use, for rewarding responses is increasing. The 2004 NSDUH estimated that 96.8 million individuals (40.2 percent of the U.S. population) have tried marijuana at least once during their lifetime. Thus, 15 percent of those who have tried marijuana on one occasion go on to use it monthly, but 85 percent of them do not.

**Monitoring the Future**

MTF (2005, *http://www.monitoringthefuture.org*) is a NIDA-sponsored annual national survey that tracks drug use trends among adolescents in the United States. The MTF surveys 8th, 10th, and 12th graders every spring in randomly selected U.S. schools. The MTF survey has been conducted since 1975 for 12th graders and since 1991 for 8th and 10th graders by the Institute for Social Research at the University of Michigan under a grant from NIDA. The 2005 sample sizes were 17,300—8th graders; 16,700—10th graders; and 15,400—12th graders. In all, a total of 49,300 students in 402 schools participated.

Since 1999, illicit drug use among teens decreased and held steady through 2005 in all three grades (Table 1). Marijuana remained the most widely used illicit drug, though its use has steadily decreased since 1999. For 2005, the annual prevalence rates for marijuana use in grades 8, 10, and 12 were, respectively, 12.2 percent, 26.6 percent, and 33.6 percent. Current monthly prevalence rates for marijuana use were 6.6 percent, 15.2 percent, and 19.8 percent. (See Table 1). According to Gruber and Pope (2002), when adolescents who used marijuana reach their late 20's, the vast majority of these individuals will have stopped using marijuana.

TABLE 1—TRENDS IN ANNUAL AND MONTHLY PREVALENCE OF USE OF VARIOUS DRUGS FOR EIGHTH, TENTH, AND TWELFTH GRADERS, FROM MONITORING THE FUTURE. PERCENTAGES REPRESENT STUDENTS IN SURVEY RESPONDING THAT THEY HAD USED A DRUG EITHER IN THE PAST YEAR OR IN THE PAST 30 DAYS

| | Annual | | | 30-Day | | |
|---|---|---|---|---|---|---|
| | 2003 | 2004 | 2005 | 2003 | 2004 | 2005 |
| Any illicit drug (a): | | | | | | |
| 8th Grade | 16.1 | 15.2 | 15.5 | 9.7 | 8.4 | 8.5 |
| 10th Grade | 32.0 | 31.1 | 29.8 | 19.5 | 18.3 | 17.3 |
| 12th Grade | 39.3 | 38.8 | 38.4 | 24.1 | 23.4 | 23.1 |
| Any illicit drug other than cannabis (a): | | | | | | |
| 8th Grade | 8.8 | 7.9 | 8.1 | 4.7 | 4.1 | 4.1 |
| 10th Grade | 13.8 | 13.5 | 12.9 | 6.9 | 6.9 | 6.4 |
| 12th Grade | 19.8 | 20.5 | 19.7 | 10.4 | 10.8 | 10.3 |
| Marijuana/hashish: | | | | | | |
| 8th Grade | 12.8 | 11.8 | 12.2 | 7.5 | 6.4 | 6.6 |
| 10th Grade | 28.2 | 27.5 | 26.6 | 17.0 | 15.9 | 15.2 |
| 12th Grade | 34.9 | 34.3 | 33.6 | 21.2 | 19.9 | 19.8 |

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

a. For 12th graders only, "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 was excluded.

**Drug Abuse Warning Network**

DAWN (2006, *http://dawninfo.samhsa.gov/*) is a national probability survey of U.S. hospitals with EDs designed to obtain information on ED visits in which recent drug use is implicated. The ED data from a representative sample of hospital emergency departments are weighted to produce national estimates. It is critical to note that DAWN data and estimates for 2004 are not comparable to those for any prior years because of vast

changes in the methodology used to collect the data. Further, estimates for 2004 are the first to be based on a new, redesigned sample of hospitals. Thus, the most recent estimates available are for 2004.

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. DAWN data do not distinguish the drug responsible for the ED visit from others used concomitantly. As stated in a recent DAWN report, "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."

For 2004, DAWN estimates a total of 1,997,993 (95 percent confidence interval [CI]: 1,708,205 to 2,287,781) drug-related ED visits for the entire United States. During this period, DAWN estimates 940,953 (CI: 773,124 to 1,108,782) drug-related ED visits involved a major drug of abuse. Thus, nearly half of all drug-related visits involved alcohol or an illicit drug. Overall, drug-related ED visits averaged 1.6 drugs per visit, including illicit drugs, alcohol, prescription and over-the-counter (OTC) pharmaceuticals, dietary supplements, and non-pharmaceutical inhalants.

Marijuana was involved in 215,665 (CI: 175,930 to 255,400) ED visits, while cocaine was involved in 383,350 (CI: 284,170 to 482,530) ED visits, heroin was involved in 162,137 (CI: 122,414 to 201,860) ED visits, and stimulants, including amphetamine and methamphetamine, were involved in 102,843 (CI: 61,520 to 144,166) ED visits. Other illicit drugs, such as PCP, MDMA, and GHB, were much less frequently associated with ED visits.

Approximately 18 percent of ED visits involving marijuana were for patients under the age of 18, whereas this age group accounts for less than 1 percent of the ED visits involving heroin/morphine and approximately 3 percent of the visits involving cocaine. Since the size of the population differs across age groups, a measure standardized for population size is useful to make comparisons. For marijuana, the rates of ED visits per 100,000 population were highest for patients aged 18 to 20 (225 ED visits per 100,000) and for patients aged 21 to 24 (190 ED visits per 100,000).

**Treatment Episode Data Set**

TEDS (TEDS, 2003; *http://oas.samhsa.gov/dasis.htm#teds2*) 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 1.8 million annual admissions to treatment for abuse of alcohol and drugs in facilities that report to individual State administrative data systems.

TEDS is an admission-based system, and TEDS admissions do not represent individuals. Thus, a given individual admitted to treatment twice within a given year would be counted as two admissions. Additionally, TEDS does not include all admissions to substance abuse treatment. TEDS includes facilities that are licensed or certified by the States 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 15.5 percent of TEDS admissions in 2003, the latest year for which data are available. Three-quarters of the individuals admitted for marijuana were male and 55 percent of the admitted individuals were white. The average age at admission was 23 years. The largest proportion (84 percent) of admissions to ambulatory treatment was for primary marijuana abuse. More than half (57 percent) of marijuana treatment admissions were referred through the criminal justice system.

Between 1993 and 2003, the percentage of admissions for primary marijuana use increased from 6.9 percent to 15.5 percent, comparable to the increase for primary opioid use from 13 percent in 1993 to 17.6 percent in 2003. In contrast, the percentage of admissions for primary cocaine use declined from 12.6 percent in 1993 to 9.8 percent in 2003, and for primary alcohol use from 56.9 percent in 1993 to 41.7 percent in 2003.

Twenty-six percent of those individuals who were admitted for primary use of marijuana reported its daily use, although 34.6 percent did not use marijuana in the past month. Nearly all (96.2 percent) of primary marijuana users utilized the drug by smoking it. Over 90 percent of primary marijuana admissions used marijuana for the first time before the age of 18.

**5. THE SCOPE, DURATION, AND SIGNIFICANCE OF ABUSE**

The fifth factor the Secretary must consider is the scope, duration, and significance of marijuana abuse. According to 2004 data from NSDUH and MTF, marijuana remains the most extensively used illegal drug in the United States, with 40.6 percent of U.S. individuals over age 12 (96.6 million) and 44.8 percent of 12th graders having used marijuana at least once in their lifetime. While the majority of individuals over age 12 (85 percent) who have used marijuana do not use the drug monthly, 14.6 million individuals (6.1 percent of the U.S. population) report that they used marijuana within the past 30 days. An examination of use among various age cohorts in NSDUH demonstrates that monthly use occurs primarily among college age individuals, with use dropping off sharply after age 25.

DAWN data show that marijuana was involved in 79,663 ED visits, which amounts to 13 percent of all drug-related ED visits. Minors accounted for 15 percent of these marijuana-related visits, making marijuana the drug most frequently associated with ED visits for individuals under the age of 18 years.

Data from TEDS show that 15.5 percent of all admissions were for primary marijuana abuse. Approximately 90 percent of these primary marijuana admissions were for individuals under the age of 18 years.

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

The sixth factor the Secretary must consider is the risk marijuana poses to the public health. The risk to the public health as measured by emergency room episodes, marijuana-related deaths, and drug treatment admissions is discussed in full under Factors 1, 4, and 5, above. Accordingly, Factor 6 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 use among others. FDA-approved drug products can produce adverse events (or "side effects") in some individuals even at doses in the therapeutic range. When determining whether a drug product is safe and effective for any indication, FDA performs an extensive 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 FDA-approved for any medicinal use, any potential benefits attributed to marijuana use have not been found to be outweighed by the risks. However, cannabinoids are generally potent psychoactive substances and are pharmacologically active on multiple organ systems.

The discussion of marijuana's central nervous system, cognitive, cardiovascular, autonomic, respiratory, and immune system effects are fully discussed under Factor 2. 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 (Institute of Medicine, 1999).

**Risks from acute use of marijuana**

Acute use of marijuana impairs psychomotor performance, including performance of complex tasks, which makes it inadvisable to operate motor vehicles or heavy equipment after using marijuana (Ramaekers et al., 2004). Dysphoria and psychological distress, including prolonged anxiety reactions, are potential responses in a minority of individuals who use marijuana (Haney et al., 1999).

**Risks from chronic use of marijuana**

Chronic exposure to marijuana smoke is considered to be comparable to tobacco smoke with respect to increased risk of cancer, lung damage, and poor pregnancy outcome. Although a distinctive marijuana withdrawal syndrome has been identified, indicating that marijuana produces physical dependence, this phenomenon is mild and short-lived (Budney et al., 2004), as described above under Factor 2.

The Diagnostic and Statistical Manual (DSM–IV–TR, 2000) of the 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

The seventh factor the Secretary must consider is marijuana's psychic or physiologic dependence liability. Physical dependence is a state of adaptation manifested by a drug class-specific withdrawal syndrome produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist (American Academy of Pain Medicine, American Pain Society and American Society of Addiction Medicine consensus document, 2001). Long-term, regular use of marijuana can lead to physical dependence and withdrawal following discontinuation as well as psychic addiction or dependence. The marijuana withdrawal syndrome consists of symptoms such as restlessness, mild agitation, insomnia, nausea, and cramping that may resolve after 4 days, and may require in-hospital treatment. It is distinct from the withdrawal syndromes associated with alcohol and heroin use (Budney et al., 1999; Haney et al., 1999). Lane and Phillips-Bute (1998) describes milder cases of dependence including symptoms that are comparable to those from caffeine withdrawal, including decreased vigor, increased fatigue, sleepiness, headache, and reduced ability to work. The marijuana withdrawal syndrome has been reported in adolescents who were admitted for substance abuse treatment or in individuals who had been given marijuana on a daily basis during research conditions. Withdrawal symptoms can also be induced in animals following administration of a cannabinoid antagonist after chronic delta$^9$-THC administration (Breivogel et al., 2003).

Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time (American Academy of Pain Medicine, American Pain Society and American Society of Addiction Medicine consensus document, 2001). Tolerance can develop to marijuana-induced cardiovascular and autonomic changes, decreased intraocular pressure, sleep and sleep EEG, and 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.

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

The eighth factor the Secretary must consider is whether marijuana is an immediate precursor of a controlled substance. Marijuana is not an immediate precursor of another controlled substance.

## RECOMMENDATION

After consideration of the eight factors discussed above, HHS recommends that marijuana remain in Schedule I of the CSA. Marijuana meets the three criteria for placing a substance in Schedule I of the CSA under 21 U.S.C. 812(b)(1):

### 1) Marijuana has a high potential for abuse:

The large number of individuals using marijuana on a regular basis, its widespread use, and the vast amount of marijuana that is available for illicit use are indicative of the high abuse potential for marijuana. Approximately 14.6 million individuals in the United States (6.1 percent of the U.S. population) used marijuana monthly in 2003. A 2003 survey indicates that by 12th grade, 33.6 percent of students report having used marijuana in the past year, and 19.8 percent report using it monthly. In Q3 to Q4 2003, 79,663 ED visits were marijuana-related, representing 13 percent of all drug-related episodes. Primary marijuana use accounted for 15.5 percent of admissions to drug treatment programs in 2003. Marijuana has dose-dependent reinforcing effects, as demonstrated by data that humans prefer higher doses of marijuana to lower doses. In addition, there is evidence that marijuana use can result in psychological dependence in at risk individuals.

### 2) Marijuana has no currently accepted medical use in treatment in the United States:

The FDA has not yet approved an NDA for marijuana. The opportunity for scientists to conduct clinical research with marijuana exists under the HHS 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 structures 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 NDA-quality 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. Finally, the scientific evidence regarding the safety or efficacy of marijuana is typically available only in summarized form, such as in a paper published in the medical literature, rather than in a raw data format. As such, there is no opportunity for adequate scientific scrutiny of whether the data demonstrate safety or efficacy.

Alternately, a drug can be considered to have "a currently accepted medical use with severe restrictions" (21 U.S.C. 812(b)(2)(B)), as allowed under the stipulations for a Schedule II drug. However, as stated above, a material conflict of opinion among experts precludes a finding that marijuana has been accepted by qualified experts, even under conditions where its use is severely restricted. To date, 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" or a "currently accepted medical use with severe restrictions."

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

At present, there are no FDA-approved marijuana products, nor is marijuana under NDA evaluation at the FDA for any indication. Marijuana does not have a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions. The Center for Medicinal Cannabis Research in California, among others, is conducting research with marijuana at the IND level, but these studies have not yet progressed to the stage of submitting an NDA. Thus, at this time, the known risks of marijuana use have

not been shown to be outweighed by specific benefits in well-controlled clinical trials that scientifically evaluate safety and efficacy.

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, HHS concludes that, even under medical supervision, marijuana has not been shown at present to have an acceptable level of safety.

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**Marijuana**

**Scheduling Review Document: Eight Factor Analysis**

*Drug and Chemical Evaluation Section*
*Office of Diversion Control*
*Drug Enforcement Administration, April 2011*

## INTRODUCTION

On October 9, 2002, the Coalition for Rescheduling Cannabis submitted a petition to the Drug Enforcement Administration (DEA) to initiate proceedings for a repeal of the rules or regulations that place marijuana [3] in schedule I of the Controlled Substances Act (CSA). The petition requests that marijuana be rescheduled as "cannabis" in either schedule III, IV, or V of the CSA. The petitioner claims that:

1. Cannabis has an accepted medical use in the United States;

2. Cannabis is safe for use under medical supervision;

3. Cannabis has an abuse potential lower than schedule I or II drugs; and

4. Cannabis has a dependence liability that is lower than schedule I or II drugs.

The DEA accepted this petition for filing on April 3, 2003. In accordance with 21 U.S.C. 811(b), after gathering the necessary data, the DEA requested a medical and scientific evaluation and scheduling recommendation for cannabis from the Department of Health and Human Services (DHHS) on July 12, 2004. On December 6, 2006, the DHHS provided its scientific and medical evaluation titled *Basis for the Recommendation for Maintaining Marijuana in Schedule I of the Controlled Substances Act* and recommended that marijuana continue to be controlled in schedule I of the CSA.

The CSA requires DEA to determine whether the DHHS scientific and medical evaluation and scheduling recommendation and "all other relevant data" constitute substantial evidence that the drug should be rescheduled as proposed in the petition. 21 U.S.C. 811(b). This document is prepared accordingly.

The Attorney General "may by rule" transfer a drug or other substance between schedules if he finds that such drug or other substance has a potential for abuse, and makes with respect to such drug or other substance the findings prescribed by subsection (b) of Section 812 for the schedule in which such drug is to be placed. 21 U.S.C. 811(a)(1). In order for a substance to be placed in schedule I, the Attorney General must find that:

A. The drug or other substance has a high potential for abuse.

B. The drug or other substance has no currently accepted medical use in treatment in the United States.

C. There is a lack of accepted safety for use of the drug or other substance under medical supervision.

21 U.S.C. 812(b)(1)(A)–(C). To be classified in one of the other schedules (II through V), a drug of abuse must have either a "currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions." 21 U.S.C. 812(b)(2)–(5). If a controlled substance has no such currently accepted medical use, it must be placed in schedule I. *See* Notice of Denial of Petition, 66 FR 20038, 20038 (Apr. 18, 2001) ("Congress established only one schedule—schedule I—for drugs of abuse with 'no currently accepted medical use in treatment in the United States' and 'lack of accepted safety for use . . . under medical supervision.'").

In deciding whether to grant a petition to initiate rulemaking proceedings with respect to a particular drug, DEA must determine whether there is sufficient evidence to conclude that the drug meets the criteria for placement in another schedule based on the criteria set forth in 21 U.S.C. 812(b). To do so, the CSA requires that DEA and DHHS consider eight factors as specified in 21 U.S.C. 811(c). This document is organized according to these eight factors.

With specific regard to the issue of whether the drug has a currently accepted medical use in treatment in the United States, DHHS states that the FDA has not evaluated nor approved a new drug application (NDA) for marijuana. The long-established factors applied by the DEA for determining whether a drug has a "currently accepted medical use" under the CSA are:

[3] The Controlled Substances Act (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 there from), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination. 21 U.S.C. 802(16).

Note that "marihuana" is the spelling originally used in the CSA. This document uses the spelling that is more common in current usage, "marijuana."

1. The drug's chemistry must be known and reproducible;
2. There must be adequate safety studies;
3. There must be adequate and well-controlled studies proving efficacy;
4. The drug must be accepted by qualified experts; and
5. The scientific evidence must be widely available.

57 FR 10,499, 10,506 (1992); *Alliance for Cannabis Therapeutics v. DEA*, 15 F.3d 1131, 1135 (D.C. Cir. 1994) (*ACT*) (upholding these factors as valid criteria for determining "accepted medical use"). A drug will be deemed to have a currently accepted medical use for CSA purposes only if all five of the foregoing elements are demonstrated. This test is considered here under the third factor.

Accordingly, as the eight factor analysis sets forth in detail below, the evidence shows:

1. *Actual or relative potential for abuse.* Marijuana has a high abuse potential. It is the most widely used illicit substance in the United States. Preclinical and clinical data show that it has reinforcing effects characteristic of drugs of abuse. National databases on actual abuse show marijuana is the most widely abused drug, including significant numbers of substance abuse treatment admissions. Data on marijuana seizures show widespread availability and trafficking.

2. *Scientific evidence of its pharmacological effect.* The scientific understanding of marijuana, cannabinoid receptors, and the endocannabinoid system has improved. Marijuana produces various pharmacological effects, including subjective (e.g., euphoria, dizziness, disinhibition), cardiovascular, acute and chronic respiratory, immune system, cognitive impairment, and prenatal exposure effects as well as possible increased risk of schizophrenia among those predisposed to psychosis.

3. *Current scientific knowledge.* There is no currently accepted medical use for marijuana in the United States. Under the five-part test for currently accepted medical use approved in *ACT*, 15 F.3d at 1135, there is no complete scientific analysis of marijuana's chemical components; there are no adequate safety studies; there are no adequate and well-controlled efficacy studies; there is not a consensus of medical opinion concerning medical applications of marijuana; and the scientific evidence regarding marijuana's safety and efficacy is not widely available. While a number of states have passed voter referenda or legislative actions authorizing the use of marijuana for medical purposes, this does not establish a currently accepted medical use under federal law. To date, scientific and medical research has not progressed to the point that marijuana has a currently accepted medical use, even under conditions where its use is severely restricted.

4. *History and current pattern of abuse.* Marijuana use has been relatively stable from 2002 to 2009, and it continues to be the most widely used illicit drug. In 2009, there were 16.7 million current users. There were also 2.4 million new users, most of whom were less than 18 years of age. During the same period, marijuana was the most frequently identified drug exhibit in federal, state, and local laboratories. High consumption of marijuana is fueled by increasing amounts of both domestically grown and illegally smuggled foreign source marijuana, and an increasing percentage of seizures involve high potency marijuana.

5. *Scope, duration, and significance of abuse.* Abuse of marijuana is widespread and significant. In 2008, for example, an estimated 3.9 million people aged 12 or older used marijuana on a daily or almost daily basis over a 12-month period. In addition, a significant proportion of all admissions for treatment for substance abuse are for primary marijuana abuse: in 2007, 16 percent of all admissions were for primary marijuana abuse, representing 287,933 individuals. Of individuals under the age of 19 admitted to substance abuse treatment, more than half were treated for primary marijuana abuse.

6. *Risk, if any, to public health.* Together with the health risks outlined in terms of pharmacological effects above, public health risks from acute use of marijuana include impaired psychomotor performance, including impaired driving, and impaired performance on tests of learning and associative processes. Public health risks from chronic use of marijuana include respiratory effects, physical dependence, and psychological problems.

7. *Psychic or physiological dependence liability.* Long-term, regular use of marijuana can lead to physical dependence and withdrawal following discontinuation, as well as psychic addiction or dependence.

8. *Immediate precursor.* Marijuana is not an immediate precursor of any controlled substance.

This review shows, in particular, that the evidence is insufficient with respect to the specific issue of whether marijuana has a currently accepted medical use under the five-part test. The evidence was insufficient in this regard on the prior two occasions when DEA considered petitions to reschedule marijuana in 1992 (57 FR 10499)[4] and in 2001 (66 FR 20038).[5] Little has changed since then with respect to the lack of clinical evidence necessary to establish that marijuana has a currently accepted medical use: only a limited number of FDA-approved Phase 1 clinical investigations have been carried out, and there have been no studies that have scientifically assessed the efficacy and full safety profile of marijuana for any medical condition.[6] The limited existing clinical evidence is not adequate to warrant rescheduling of marijuana under the CSA.

To the contrary, the data in this Scheduling Review document show that marijuana continues to meet the criteria for schedule I control under the CSA for the following reasons:

1. Marijuana has a high potential for abuse.
2. Marijuana has no currently accepted medical use in treatment in the United States.
3. Marijuana lacks accepted safety for use under medical supervision.

## FACTOR 1: THE DRUG'S ACTUAL OR RELATIVE POTENTIAL FOR ABUSE

Marijuana is the most commonly abused illegal drug in the United States. It is also the most commonly used illicit drug by American high-schoolers. Marijuana is the most frequently identified drug in state, local and federal forensic laboratories, with increasing amounts both of domestically grown and of illicitly smuggled marijuana. Marijuana's main psychoactive ingredient, $\Delta^9$-THC, is an effective reinforcer in laboratory animals, including primates and rodents. These animal studies both predict and support the observations that $\Delta^9$-THC, whether smoked as marijuana or administered by other routes, produces reinforcing effects in humans. Such reinforcing effects can account for the repeated abuse of marijuana.

### A. Indicators of Abuse Potential

DHHS has concluded in its document, "Basis for the Recommendation for Maintaining Marijuana in Schedule I of the Controlled Substances Act", that marijuana has a high potential for abuse. The finding of "abuse potential" is critical for control under the Controlled Substances Act (CSA). Although the term is not defined in the CSA, guidance in determining abuse potential is provided in the legislative history of the Act (Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91–144, 91st Cong., Sess.1 (1970), reprinted in 1970 U.S.C.C.A.N. 4566, 4603). Accordingly, the following items are indicators that a drug or other substance has potential for abuse:

- There is evidence that individuals are taking the drug or other substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community; or
- There is significant diversion of the drug or other substance from legitimate drug channels; or
- Individuals are taking the drug or substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs; or
- The drug is a new drug so related in its action to a drug or other substance already listed as having a potential for abuse to make it likely that the drug substance will have the same potential for abuse as such drugs, thus

[4] *Petition for review dismissed, Alliance for Cannabis Therapeutics v. DEA*, 15 F.3d 1131 (D.C. Cir. 1994).

[5] *Petition for review dismissed, Gettman v. DEA*, 290 F.3d 430 (D.C. Cir. 2002).

[6] Clinical trials generally proceed in three phases. *See* 21 CFR 312.21 (2010). Phase I trials encompass initial testing in human subjects, generally involving 20 to 80 patients. Id. They are designed primarily to assess initial safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary studies of potential therapeutic benefit. 62 FR 66113, 1997. Phase II and Phase III studies involve successively larger groups of patients: usually no more than several hundred subjects in Phase II, and usually from several hundred to several thousand in Phase III. 21 CFR 312.21. These studies are designed primarily to explore (Phase II) and to demonstrate or confirm (Phase III) therapeutic efficacy and benefit in patients. 62 FR 66113, 1997. *See also Riegel v. Medtronic, Inc.*, 128 S.Ct. 999, 1018–19 n.15 (2008) (Ginsburg, J., dissenting).

making it reasonable to assume that there may be significant diversion 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. Of course, evidence of actual abuse of a substance is indicative that a drug has a potential for abuse.

After considering the above items, DHHS has found that marijuana has a high potential for abuse.

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

Marijuana is the most highly used illicit substance in the United States. Smoked marijuana exerts a number of cardiovascular and respiratory effects, both acutely and chronically and can cause chronic bronchitis and inflammatory abnormalities of the lung tissue. Marijuana's main psychoactive ingredient $\Delta^9$-THC alters immune function and decreases resistance to microbial infections. The cognitive impairments caused by marijuana use that persist beyond behaviorally detectable intoxication may have significant consequences on workplace performance and safety, academic achievement, and automotive safety, and adolescents may be particularly vulnerable to marijuana's cognitive effects. Prenatal exposure to marijuana was linked to children's poorer performance in a number of cognitive tests. Data on the extent and scope of marijuana abuse are presented under factors 4 and 5 of this analysis. DHHS's discussion of the harmful health effects of marijuana and additional information gathered by DEA are presented under factor 2, and the assessment of risk to the public health posed by acute and chronic marijuana abuse is presented under factor 6 of this analysis.

2. There is significant diversion of the drug or other substance from legitimate drug channels.

DHHS states that at present, marijuana is legally available through legitimate channels for research only and thus has a limited potential for diversion. (DEA notes that while a number of states have passed voter referenda or legislative actions authorizing the use of marijuana for medical purposes, this does not establish a currently accepted medical use under federal law.) In addition, the lack of significant diversion of investigational supplies may result from the ready availability of illicit cannabis of equal or greater quality.

DEA notes that the magnitude of the demand for illicit marijuana is evidenced by information from a number of databases presented under factor 4. Briefly, marijuana is the most commonly abused illegal drug in the United States. It is also the most commonly used illicit drug by American high-schoolers. Marijuana is the most frequently identified drug in state, local, and federal forensic laboratories, with increasing amounts both of domestically grown and of illicitly smuggled marijuana. An observed increase in the potency of seized marijuana also raises concerns.

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

16.7 million adults over the age of 12 reported having used marijuana in the past month, according to the 2009 National Survey on Drug Use and Health (NSDUH), as further described later in this factor. DHHS states in its 2006 analysis of the petition that the FDA has not evaluated or approved a new drug application (NDA) for marijuana for any therapeutic indication, although several investigational new drug (IND) applications are currently active. Based on the large number of individuals who use marijuana, DHHS concludes 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.

4. The drug is a new drug so related in its action to a drug or other substance already listed as having a potential for abuse to make it likely that the drug substance will have the same potential for abuse as such drugs, 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. Of course, evidence of actual abuse of a substance is indicative that a drug has a potential for abuse.

Marijuana is not a new drug. Marijuana's primary psychoactive ingredient delta-9-tetrahydrocannabinol ($\Delta^9$-THC) is controlled in schedule I of the CSA. DHHS states that there are two drug products containing cannabinoid compounds that are structurally related to the active components in marijuana. Both are controlled under the CSA. Marinol is a schedule III drug product containing synthetic $\Delta^9$-THC, known generically as dronabinol, formulated in sesame oil in soft gelatin capsules. Marinol was approved by the FDA in 1985 for the treatment of two medical conditions: nausea and vomiting associated with cancer chemotherapy in patients that had failed to respond adequately to conventional anti-emetic treatments, and for the treatment of anorexia associated with weight loss in patients with acquired immunodeficiency syndrome (AIDS). Cesamet is a drug product containing the schedule II substance, nabilone, that was approved for marketing by the FDA in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy. All other structurally related cannabinoids in marijuana are already listed as Schedule I drugs under the CSA.

In addition, DEA notes that marijuana and its active ingredient $\Delta^9$-THC are related in their action to other controlled drugs of abuse when tested in preclinical and clinical tests of abuse potential. Data showing that marijuana and $\Delta^9$-THC exhibit properties common to other controlled drugs of abuse in those tests are described below in this factor.

In summary, examination of the indicators set forth in the legislative history of the CSA demonstrates that marijuana has a high potential for abuse. Indeed, marijuana is abused in amounts sufficient to create hazards to public health and safety; there is significant trafficking of the substance; individuals are using marijuana on their own initiative, for the vast majority, rather than on the basis of medical advice; and finally, marijuana exhibits several properties common to those of drugs already listed as having abuse potential.

The petitioner states that, "widespread use of cannabis is not an indication of its abuse potential [...] ." (Exh. C, Section IV(15), pg. 87).

To the contrary, according to the indicators set forth in the legislative history of the CSA as described above, the fact that "Individuals are taking the drug or substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs" is indeed one of several indicators that a drug has high potential for abuse.

**B. Abuse Liability Studies**

In addition to the indicators suggested by the CSA's legislative history, data as to preclinical and clinical abuse liability studies, as well as actual abuse, including clandestine manufacture, trafficking, and diversion from legitimate sources, are considered in this factor.

Abuse liability evaluations are obtained from studies in the scientific and medical literature. There are many preclinical measures of a drug's effects that when taken together provide an accurate prediction of the human abuse liability. Clinical studies of the subjective and reinforcing effects in humans and epidemiological studies provide quantitative data on abuse liability in humans and some indication of actual abuse trends. Both preclinical and clinical studies have clearly demonstrated that marijuana and $\Delta^9$-THC possess the attributes associated with drugs of abuse: they function as a positive reinforcer to maintain drug-seeking behavior, they function as a discriminative stimulus, and they have dependence potential.

Preclinical and most clinical abuse liability studies have been conducted with the psychoactive constituents of marijuana, primarily $\Delta^9$-THC and its metabolite, 11-OH-$\Delta^9$-THC. $\Delta^9$-THC's subjective effects are considered to be the basis for marijuana's abuse liability. The following studies provide a summary of that data.

*1. Preclinical Studies*

Delta-9-THC is an effective reinforcer in laboratory animals, including primates and rodents, as these animals will self-administer $\Delta^9$-THC. These animal studies both predict and support the observations that $\Delta^9$-THC, whether smoked as marijuana or administered by other routes, produces reinforcing effects in humans. Such reinforcing effects can account for the repeated abuse of marijuana.

*a. Discriminative Stimulus Effects*

The drug discrimination paradigm is used as an animal model of human subjective effects (Solinas *et al.*, 2006). This procedure provides a direct measure of stimulus

specificity of a test drug in comparison with a known standard drug or a neutral stimulus (e.g., injection of saline water). The light-headedness and warmth associated with drinking alcohol or the jitteriness and increased heart rate associated with drinking coffee are examples of substance-specific stimulus effects. The drug discrimination paradigm is based on the ability of nonhuman and human subjects to learn to identify the presence or absence of these stimuli and to differentiate among the constellation of stimuli produced by different pharmacological classes. In drug discrimination studies, the drug stimuli function as cues to guide behavioral choice, which is subsequently reinforced with other rewards. Repeated pairing of the reinforcer with only drug-appropriate responses can engender reliable discrimination between drug and no-drug or amongst several drugs. Because some interoceptive stimuli are believed to be associated with the reinforcing effects of drugs, the drug discrimination paradigm is used to evaluate the abuse potential of new substances.

DHHS states that in the drug discrimination test, animals are trained to respond by pressing one bar when they receive the known drug of abuse and another bar when they receive placebo.

DHHS states that cannabinoids appear to provide unique discriminative stimulus effects because stimulants, non-cannabinoid hallucinogens, opioids, benzodiazepines, barbiturates, NMDA antagonists and antipsychotics do not fully substitute for $\Delta^9$-THC (Browne and Weissman, 1981; Balster and Prescott, 1992, Gold *et al.*, 1992; Barrett *et al.*, 1995; Wiley *et al.*, 1995). Animals, including monkeys and rats (Gold et al., 1992), as well as humans (Chait *et al.*, 1988), can discriminate cannabinoids from other drugs or placebo.

DEA notes several studies that show that the discriminative stimulus effects of $\Delta^9$-THC are mediated via a cannabinoid receptor, specifically, the $CB_1$ receptor subtype, and that the $CB_1$ antagonist rimonabant (SR 141716A) antagonizes the discriminative stimulus effects of $\Delta^9$-THC in several species (Pério *et al.*, 1996; Mansbach *et al.*, 1996; Järbe *et al.*, 2001). The subjective effects of marijuana and $\Delta^9$-THC are, therefore, mediated by a neurotransmitter system in the brain that is specific to $\Delta^9$-THC and cannabinoids.

*b. Self-Administration Studies*

Self-administration is a behavioral assay that measures the rewarding effects of a drug that increase the likelihood of continued drug-taking behavior. Drugs that are self-administered by animals are likely to produce rewarding effects in humans. A strong correlation exists between drugs and other substances that are abused by humans and those that maintain self-injection in laboratory animals (Schuster and Thompson, 1969; Griffiths *et al.*, 1980). As a result, intravenous self-injection of psychoactive substances in laboratory animals is considered to be useful for the prediction of human abuse liability of these compounds (Johanson and Balster, 1978; Collins et al., 1984).

DHHS states that self-administration of hallucinogenic-like drugs, such as cannabinoids, lysergic acid diethylamide (LSD), and mescaline, has been difficult to demonstrate in animals (Yanagita, 1980). DHHS further states that an inability to establish self-administration has no practical importance in the assessment of abuse potential, because it is known that humans voluntarily consume a particular drug (such as cannabis) for its pleasurable effects.

DHHS states that the experimental literature generally reports that naïve animals will not self-administer cannabinoids unless they have had previous experience with other drugs of abuse, however, animal research in the past decade has provided several animal models of reinforcement by cannabinoids to allow for pre-clinical research into cannabinoids' reinforcing effects. Squirrel monkeys trained to self-administer intravenous cocaine will continue to respond at the same rate as when $\Delta^9$-THC is substituted for cocaine, at doses that are comparable to those used by humans who smoke marijuana (Tanda *et al.*, 2000). This effect is blocked by the cannabinoid receptor antagonist, SR 141716. Squirrel monkeys without a history of any drug exposure can be successfully trained to self-administer $\Delta^9$-THC intravenously (Justinova *et al.*, 2003). The maximal rate of responding is 4 µg/kg/injection, which is 2–3 times greater than that observed in previous studies using cocaine-experienced monkeys. Rats will self-administer $\Delta^9$-THC when it is applied intracerebroventricularly (i.c.v.), but only at the lowest doses tested (0.01:–0.02/µg/infusion) (Braida *et al.*, 2004). This effect is antagonized by the cannabinoid antagonist SR141716 and by the opioid antagonist naloxone (Braida et al., 2004). Additionally, mice will self-administer WIN 55212, a synthetic $CB_1$ receptor agonist with a non-cannabinoid structure (Martellotta *et al.*, 1998).

DEA notes a study showing that the opioid antagonist naltrexone reduces the self-administration responding for $\Delta^9$-THC in squirrel monkeys (Justinova *et al.*, 2004). These investigators, using second-order schedules of drug-seeking procedures, also showed that pre-session administration of $\Delta^9$-THC and other cannabinoid agonists, or morphine, but not cocaine, reinstates the $\Delta^9$-THC seeking behavior following a period of abstinence (Justinova *et al.*, 2008). Furthermore, the endogenous cannabinoid anandamide and its synthetic analog methanandamide are self-administered by squirrel monkeys, and $CB_1$ receptor antagonism blocks the reinforcing effect of both substances (Justinova *et al.*, 2005).

c. Place Conditioning Studies

Conditioned place preference (CPP) is another behavioral assay used to determine if a drug has rewarding properties. In this test, animals in a drug-free state are given the opportunity to spend time in two distinct environments: one where they previously received a drug and one where they received a placebo. If the drug is reinforcing, animals in a drug-free state will choose to spend more time in the environment paired with the drug when both environments are presented simultaneously.

DHHS states that animals exhibit CPP to $\Delta^9$-THC, but only at the lowest doses tested (0.075–0.75 mg/kg, i.p.) (Braida *et al.*, 2004). The effect is antagonized by the cannabinoid antagonist, rimonabant, as well as the opioid antagonist, naloxone. The effect of naloxone on CPP to $\Delta^9$-THC raises the possibility that the opioid system may be involved in the rewarding properties of $\Delta^9$-THC and marijuana. DEA notes a recent review (Murray and Bevins, 2010) that further explores the currently available knowledge on $\Delta^9$-THC's ability to induce CPP and conditioned place aversion (CPA), and further supports that low doses of $\Delta^9$-THC appear to have conditioned rewarding effects, whereas higher doses have aversive effects.

*2. Clinical Studies*

DHHS states that the physiological, psychological, and behavioral effects of marijuana vary among individuals and presents a list of common responses to cannabinoids, as described in the scientific literature (Adams and Martin, 1996; Hollister, 1986, 1988; Institute of Medicine, 1982):

1. Dizziness, nausea, tachycardia, facial flushing, dry mouth and tremor 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 judgment, reduced coordination 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

These subjective responses to marijuana are pleasurable to many humans and are associated with drug-seeking and drug-taking (Maldonado, 2002). DHHS states that, as with most psychoactive drugs, an individual's response to marijuana can be influenced by a person's medical/psychiatric history as well as their experience with drugs. Frequent marijuana users (used more than 100 times) were better able to identify a drug effect from low-dose $\Delta^9$-THC than infrequent users (used less than 10 times) and were less likely to experience sedative effects from the drug (Kirk and de Wit, 1999). However, dose preferences have been demonstrated for marijuana in which higher doses (1.95 percent $\Delta^9$-THC) are preferred over lower doses (0.63 percent $\Delta^9$-THC) (Chait and Burke, 1994).

DEA notes that an extensive review of the reinforcing effects of marijuana in humans was included in DEA/DHHS's prior review of

marijuana (Notice of Denial of Petition, 66 FR 20038, 2001). While additional studies have been published on the reinforcing effects of marijuana in humans (e.g., see review by Cooper and Haney, 2009), they are consistent with the information provided in DEA/DHHS's prior review of this matter. Excerpts are provided below, with some citations omitted.

Both marijuana and THC can serve as positive reinforcers in humans. Marijuana and $\Delta^9$-THC produced profiles of behavioral and subjective effects that were similar regardless of whether the marijuana was smoked or taken orally, as marijuana in brownies, or orally as THC-containing capsules, although the time course of effects differed substantially. There is a large clinical literature documenting the subjective, reinforcing, discriminative stimulus, and physiological effects of marijuana and THC and relating these effects to the abuse potential of marijuana and THC (e.g., Chait *et al.*, 1988; Lukas *et al.*, 1995; Kamien et al., 1994; Chait and Burke, 1994; Chait and Pierri, 1992; Foltin *et al.*, 1990; Azorlosa *et al.*, 1992; Kelly et al., 1993, 1994; Chait and Zacny, 1992; Cone *et al.*, 1988; Mendelson and Mello, 1984).

These listed studies represent a fraction of the studies performed to evaluate the abuse potential of marijuana and THC. In general, these studies demonstrate that marijuana and THC dose-dependently increases heart rate and ratings of "high" and "drug liking", and alters behavioral performance measures (e.g., Azorlosa *et al.*, 1992; Kelly et al., 1993, 1994; Chait and Zacny, 1992; Kamien *et al.*, 1994; Chait and Burke, 1994; Chait and Pierri, 1992; Foltin *et al.*, 1990; Cone *et al.*, 1988; Mendelson and Mello, 1984). Marijuana also serves as a discriminative stimulus in humans and produces euphoria and alterations in mood. These subjective changes were used by the subjects as the basis for the discrimination from placebo (Chait *et al.*, 1988).

In addition, smoked marijuana administration resulted in multiple brief episodes of euphoria that were paralleled by rapid transient increases in EEG alpha power (Lukas *et al.*, 1995); these EEG changes are thought to be related to CNS processes of reinforcement (Mello, 1983).

To help elucidate the relationship between the rise and fall of plasma THC and the self-reported psychotropic effects, Harder and Rietbrock (1997) measured both the plasma levels of THC and the psychological "high" obtained from smoking a marijuana cigarette containing 1% THC. As can be seen from these data, a rise in plasma THC concentrations results in a corresponding increase in the subjectively reported feelings of being "high". However, as THC levels drop the subjectively reported feelings of "high" remain elevated. The subjective effects seem to lag behind plasma THC levels. Similarly, Harder and Rietbrock compared lower doses of 0.3% THC-containing and 0.1% THC-containing cigarettes in human subjects.

As can be clearly seen from these data, even low doses of marijuana, containing 1%, 0.3% and even 0.1% THC, typically referred to as "non-active", are capable of producing subjective reports and physiological markers of being "high'.

THC and its major metabolite, 11-OH-THC, have similar psychoactive and pharmacokinetic profiles in man (Wall *et al.*, 1976; DiMarzo *et al.*, 1998; Lemberger *et al.*, 1972). Perez-Reyes *et al.* (1972) reported that THC and 11-OH-THC were equipotent in generating a "high" in human volunteers. However, the metabolite, 11-OH-THC, crosses the blood-brain barrier faster than the parent THC compound (Ho *et al.*, 1973; Perez-Reyes et al., 1976). Therefore, the changes in THC plasma concentrations in humans may not be the best predictive marker for the subjective and physiological effects of marijuana in humans. Cocchetto *et al.* (1981) have used hysteresis plots to clearly demonstrate that plasma THC concentration is a poor predictor of simultaneous occurring physiological (heart rate) and psychological ("high") pharmacological effects. Cocchetto *et al.* demonstrated that the time course of tachycardia and psychological responses lagged behind the plasma THC concentration-time profile. As recently summarized by Martin and Hall (1997, 1998)

"There is no linear relationship between blood [THC] levels and pharmacological effects with respect to time, a situation that hampers the prediction of cannabis-induced impairment based on THC blood levels (p90)".

Drug craving is an urge or desire to re-experience the drug's effects and is considered to be one component of drug dependence, in part responsible for continued drug use and relapse after treatment or during periods of drug abstinence. DEA notes that Budney and colleagues (1999) reported that 93 percent of marijuana-dependent adults seeking treatment reported experiencing mild craving for marijuana, and 44 percent rated their past craving as severe. Heishman and colleagues developed in 2001 a Marijuana Craving Questionnaire (MCQ). When they administered their MCQ to 217 current marijuana smokers who were not attempting to quit or reduce their marijuana use, they found that marijuana craving can be measured in current smokers that are not seeking treatment. Most subjects (83 percent) reported craving marijuana 1–5 times per day, and 82 percent reported that each craving episode lasted 30 minutes or less. Furthermore, they determined that craving for marijuana can be characterized by four components: (1) compulsivity, an inability to control marijuana use; (2) emotionality, use of marijuana in anticipation of relief from withdrawal or negative mood; (3) expectancy, anticipation of positive outcomes from smoking marijuana; and (4) purposefulness, intention and planning to use marijuana for positive outcomes.

### C. Actual Abuse of Marijuana—National Databases Related to Marijuana Abuse and Trafficking

Marijuana use has been relatively stable from 2002 to 2008, and it continues to be the most widely used illicit drug. Evidence of actual abuse can be defined by episodes/mentions in databases indicative of abuse/dependence. DHHS provided in its 2006 documents data relevant to actual abuse of marijuana including data from the National Survey on Drug Use and Health (NSDUH; formally known as the National Household Survey on Drug Abuse), the Drug Abuse Warning Network (DAWN), Monitoring the Future (MTF) survey, and the Treatment Episode Data Set (TEDS). These data collection and reporting systems provide quantitative data on many factors related to abuse of a particular substance, including incidence, pattern, consequence and profile of the abuser of specific substances. DEA provides here updates to these databases as well as additional data on trafficking and illicit availability of marijuana using information from databases it produces, such as the National Forensic Laboratory Information System (NFLIS), the System to Retrieve Information from Drug Evidence (STRIDE) and the Federal-wide Drug Seizure System (FDSS), as well as other sources of data specific to marijuana, including the Potency Monitoring Project and the Domestic Cannabis Eradication and Suppression Program (DCE/SP).

#### *1. National Survey on Drug Use and Health (NSDUH)*

The National Survey on Drug Use and Health, formerly known as the National Household Survey on Drug Abuse (NHSDA), is conducted annually by the Department of Health and Human Service's Substance Abuse and Mental Health Services Administration (SAMHSA). It is the primary source of estimates of the prevalence and incidence of pharmaceutical drugs, illicit drugs, alcohol, and tobacco use in the United States. The survey is based on a nationally representative sample of the civilian, non-institutionalized population 12 years of age and older. The survey excludes homeless people who do not use shelters, active military personnel, and residents of institutional group quarters such as jails and hospitals.

According to the 2009 NSDUH report, marijuana was the most commonly used illicit drug (16.7 million past month users) in the United States. (Note that NSDUH figures on marijuana use include hashish use; the relative proportion of hashish use to marijuana use is very low). Marijuana was also the most widely abused drug. The 2009 NSDUH report stated that 4.3 million persons were classified with substance dependence or abuse of marijuana in the past year based on criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM–IV). Among persons aged 12 or older, the past month marijuana use in 2009 (6.6 percent) was statistically significantly higher than in 2008 (6.1 percent). In 2008, among adults aged 18 or older who first tried marijuana at age 14 or younger, 13.5 percent were classified with illicit drug dependence or abuse, higher than the 2.2 percent of adults who had first used marijuana at age 18 or older.

In 2008, among past year marijuana users aged 12 or older, 15.0 percent used marijuana on 300 or more days within the previous 12 months. This translates into 3.9 million people using marijuana on a daily or almost

daily basis over a 12-month period, higher than the estimate of 3.6 million (14.2 percent of past year users) in 2007. Among past month marijuana users, 35.7 percent (5.4 million) used the drug on 20 or more days in the past month.

*2. Monitoring the Future*

Monitoring the Future (MTF) is a national survey conducted by the Institute for Social Research at the University of Michigan under a grant from the National Institute on Drug Abuse (NIDA) that tracks drug use trends among American adolescents in the 8th, 10th, and 12th grades. Marijuana was the most commonly used illicit drug reported in the 2010 MTF report. Approximately 8.0 percent of 8th graders, 16.7 percent of the 10th graders, and 21.4 percent of 12th graders surveyed in 2010 reported marijuana use during the past month prior to the survey. Monitoring the Future participants reported a statistically significant increase of daily use in the past month in 2010, compared to 2009, 1.2 percent, 3.3 percent, and 6.1 percent of eighth, tenth and twelfth graders, respectively.

*3. DAWN ED (Emergency Department)*

The Drug Abuse Warning Network (DAWN) is a public health surveillance system that monitors drug-related hospital emergency department (ED) visits to track the impact of drug use, misuse, and abuse in the United States. DAWN provides a picture of the impact of drug use, misuse, and abuse on metropolitan areas and across the nation. DAWN gathers data on drug abuse-related ED visits from a representative sample of hospitals in the coterminous United States. DAWN ED gathers data on emergency department visits relating to substance use including, but not limited to, alcohol, illicit drugs, and other substances categorized as psychotherapeutic, central nervous system, respiratory, cardiovascular, alternative medication, anti-infective, hormone, nutritional product and gastrointestinal agents. For the purposes of DAWN, the term "drug abuse" applies if the following conditions are met: (1) the case involved at least one of the following: use of an illegal drug; use of a legal drug contrary to directions; or inhalation of a non-pharmaceutical substance and (2) the substance was used for one of the following reasons: because of drug dependence; to commit suicide (or attempt to commit suicide); for recreational purposes; or to achieve other psychic effects.

In 2009, marijuana was involved in 376,467 ED visits, out of 1,948,312 drug-related ED visits, as estimated by DAWN ED for the entire United States. This compares to a higher number of ED visits involving cocaine (422,896), and lower numbers of ED visits involving heroin (213,118) and stimulants (amphetamine, methamphetamine) (93,562). Visits involving the other major illicit drugs, such as MDMA, GHB, LSD and other hallucinogens, PCP, and inhalants, were much less frequent, comparatively.

In young patients, marijuana is the illicit drug most frequently involved in ED visits according to DAWN estimates, with 182.2 per 100,000 population aged 12 to 17, 484.8 per 100,000 population aged 18 to 20, and 360.2 per 100,000 population aged 21 to 24.

*4. Treatment Episode Data Set (TEDS) System*

Users can become dependent on marijuana to the point that they seek treatment to stop abusing it or are referred to a drug abuse treatment program. The TEDS system is part of the SAMHSA Drug and Alcohol Services Information System. TEDS comprises data on treatment admissions that are routinely collected by states in monitoring their substance abuse treatment systems. The primary goal of the TEDS is to monitor the characteristics of treatment episodes for substances abusers. The TEDS report provides information on both the demographic and substance use characteristics of admissions to treatment for abuse of alcohol and drugs in facilities that report to individual state administrative data systems. TEDS does not include all admissions to substance abuse treatment. It includes admissions to facilities that are licensed or certified by the state substance abuse agency to provide substance abuse treatment (or are administratively tracked by the agency for other reasons). In general, facilities reporting to TEDS are those that receive state alcohol and/or drug agency funds (including federal block grant funds) for the provision of alcohol and/or drug treatment services. The primary substances reported by TEDS are alcohol, cocaine, marijuana (marijuana is considered together with hashish), heroin, other opiates, PCP, hallucinogens, amphetamines, other stimulants, tranquilizers, sedatives, inhalants and other/unknown. TEDS defines Primary Substance of Abuse as the main substance of abuse reported at the time of admission. TEDS also allows for the recording of two other substances of abuse (secondary and tertiary). A client may be abusing more than three substances at the time of admission, but only three are recorded in TEDS.

Admissions for primary abuse of marijuana/hashish accounted for 16 percent of all treatment admissions reported to the TEDS system in 2006 and 2007. In 2006, 2007 and 2008, 1,933,206, 1,920,401 and 2,016,256 people were admitted to drug and alcohol treatment in the United States, respectively. The marijuana/hashish admissions represented 16 percent (308,670), 16 percent (307,123) and 17.2 percent (346,679) of the total drug/alcohol treatment admissions in 2006, 2007 and 2008, respectively. In 2008, 65.8 percent of the individuals admitted for marijuana were aged 12–17, 18–20 and 21–25 (30.5 percent, 15.3 percent and 20.0 percent, respectively). Among the marijuana/hashish admissions in 2007 in which age of first use was reported (286,194), 25.1 percent began using marijuana at age 12 or younger.

*5. Forensic Laboratory Data*

Marijuana is widely available in the United States, fueled by increasing marijuana production at domestic grow sites as well as increasing production in Mexico and Canada. Data on marijuana seizures from federal, state, and local law enforcement laboratories have indicated that there is significant trafficking of marijuana. The National Forensic Laboratory Information System (NFLIS) is a program sponsored by the Drug Enforcement Administration's Office of Diversion Control. NFLIS compiles information on exhibits analyzed in state and local law enforcement laboratories. The System to Retrieve Information from Drug Evidence (STRIDE) is a DEA database which compiles information on exhibits analyzed in DEA laboratories. NFLIS and STRIDE together capture data for all substances reported by forensic laboratory analyses. More than 1,700 unique substances are reported to these two databases.

NFLIS showed that marijuana was the most frequently identified drug in state and local laboratories from January 2001 through December 2010. Marijuana accounted for between 34 percent and 38 percent of all drug exhibits analyzed during that time frame. Similar to NFLIS, STRIDE data showed that marijuana was the most frequently identified drug in DEA laboratories for the same reporting period. From January 2001 through December 2010, a range of between 17 percent and 21 percent of all exhibits analyzed in DEA laboratories were identified as marijuana (Table 1).

TABLE 1—MARIJUANA (OTHER THAN HASHISH) (EXHIBITS AND CASES) REPORTED BY NFLIS AND STRIDE, 2001–2010, FORENSIC LABORATORY DATA

| | NFLIS | | STRIDE | |
|---|---|---|---|---|
| | Exhibits (percent total exhibits) | Cases | Exhibits (percent total exhibits) | Cases |
| 2001 | 314,002 (37.9%) | 261,191 | 16,523 (20.7%) | 13,256 |
| 2002 | 373,497 (36.6%) | 312,161 | 14,010 (19.4%) | 11,306 |
| 2003 | 407,046 (36.7%) | 339,995 | 13,946 (19.9%) | 10,910 |
| 2004 | 440,964 (35.5%) | 371,841 | 13,657 (18.4%) | 10,569 |
| 2005 | 469,186 (33.5%) | 394,557 | 14,004 (18.3%) | 10,661 |

TABLE 1—MARIJUANA (OTHER THAN HASHISH) (EXHIBITS AND CASES) REPORTED BY NFLIS AND STRIDE, 2001–2010, FORENSIC LABORATORY DATA—Continued

| | NFLIS | | STRIDE | |
|---|---|---|---|---|
| | Exhibits (percent total exhibits) | Cases | Exhibits (percent total exhibits) | Cases |
| 2006 | 506,472 (33.6%) | 421,943 | 13,597 (18.5%) | 10,277 |
| 2007 | 512,082 (34.7%) | 423,787 | 13,504 (19.2%) | 10,413 |
| 2008 | 513,644 (35.1%) | 421,782 | 12,828 (18.8%) | 10,109 |
| 2009 | 524,827 (35.6%) | 414,006 | 12,749 (17.7%) | 10,531 |
| 2010 | 464,059 (36.3%) | 362,739 | 11,293 (16.7%) | 7,158 |

Data queried 03–04–2011.

TABLE 2—HASHISH (EXHIBITS AND CASES) REPORTED BY NFLIS AND STRIDE, 2001–2010, FORENSIC LABORATORY DATA

| | NFLIS | | STRIDE | |
|---|---|---|---|---|
| | Exhibits | Cases | Exhibits | Cases |
| 2001 | 1,689 | 1,671 | 53 | 50 |
| 2002 | 2,278 | 2,254 | 40 | 38 |
| 2003 | 2,533 | 2,503 | 48 | 42 |
| 2004 | 2,867 | 2,829 | 63 | 51 |
| 2005 | 2,674 | 2,639 | 122 | 90 |
| 2006 | 2,836 | 2,802 | 102 | 76 |
| 2007 | 3,224 | 3,194 | 168 | 122 |
| 2008 | 2,988 | 2,920 | 124 | 102 |
| 2009 | 2,952 | 2,843 | 119 | 96 |
| 2010 | 2,473 | 2,392 | 141 | 84 |

Data queried 03–04–2011.

Since 2001, the total number of exhibits and cases of marijuana and the amount of marijuana seized federally has remained high and the number of marijuana plants eradicated has considerably increased (see data from Federal-wide Drug Seizure System and Domestic Cannabis Eradication and Suppression Program below).

*6. Federal-wide Drug Seizure System*

The Federal-wide Drug Seizure System (FDSS) contains information about drug seizures made by the Drug Enforcement Administration, the Federal Bureau of Investigation, United States Customs and Border Protection, and United States Immigration and Customs Enforcement, within the jurisdiction of the United States. It also records maritime seizures made by the United States Coast Guard. Drug seizures made by other Federal agencies are included in the FDSS database when drug evidence custody is transferred to one of the agencies identified above. FDSS is now incorporated into the National Seizure System (NSS), which is a repository for information on clandestine laboratory, contraband (chemicals and precursors, currency, drugs, equipment and weapons). FDSS reports total federal drug seizures (kg) of substances such as cocaine, heroin, MDMA, methamphetamine, and cannabis (marijuana and hashish). The yearly volume of cannabis seized (Table 3), consistently exceeding a thousand metric tons per year, shows that cannabis is very widely trafficked in the United States.

TABLE 3—TOTAL FEDERAL SEIZURES OF CANNABIS

[Expressed in kg]

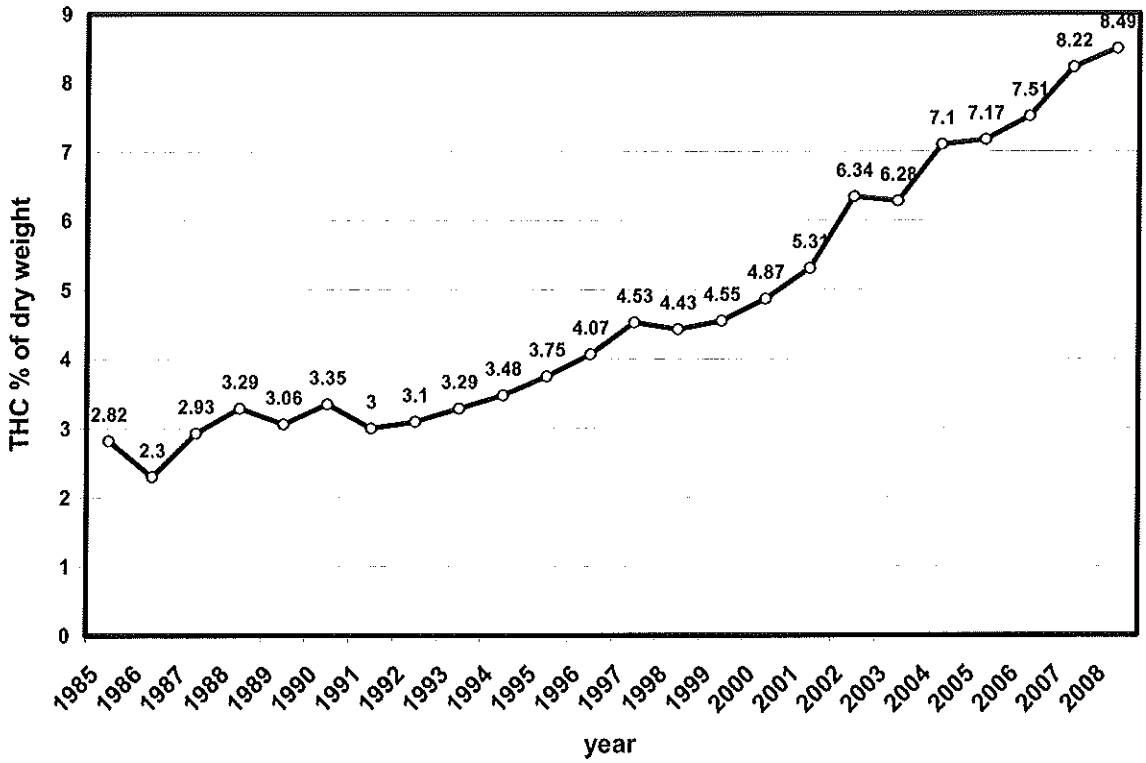
| | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2009 |
|---|---|---|---|---|---|---|---|---|---|
| Cannabis | 1,103,173 | 1,232,711 | 1,179,230 | 1,116,977 | 1,141,915 | 1,459,220 | 1,590,793 | 1,911,758 | 1,858,808 |
| Marijuana | 1,102,556 | 1,232,556 | 1,179,064 | 1,116,589 | 1,141,737 | 1,458,883 | 1,590,505 | 1,910,775 | 1,858,422 |
| Hashish | 618 | 155 | 166 | 388 | 178 | 338 | 289 | 983 | 386 |

*7. Potency Monitoring Project*

Rising availability of high potency (i.e., with high $\Delta^9$-THC concentrations) marijuana has pushed the average marijuana potency to its highest recorded level. The University of Mississippi's Potency Monitoring Project (PMP), through a contract with the National Institute on Drug Abuse (NIDA), analyzes and compiles data on the $\Delta^9$-THC concentrations of cannabis, hashish and hash oil samples provided by DEA regional laboratories and by state and local police agencies.

DEA notes studies showing that when given the choice between low- and high-potency marijuana, subjects chose the high-potency marijuana significantly more often than the low-potency marijuana (Chait and Burke, 1994), supporting the hypothesis that the reinforcing effects of marijuana, and possibly its abuse liability, are positively related to THC content.

**Figure 1. Average Percentage of $\Delta^9$-THC in Samples of Seized Marijuana (1985 –2008) (Source: The University of Mississippi Potency Monitoring Project)**




*8. The Domestic Cannabis Eradication and Suppression Program*

The Domestic Cannabis Eradication and Suppression Program (DCE/SP) was established in 1979 to reduce the supply of domestically cultivated marijuana in the United States. The program was designed to serve as a partnership between federal, state, and local agencies. Only California and Hawaii were active participants in the program at its inception. However, by 1982 the program had expanded to 25 states and by 1985 all fifty states were participants. Cannabis is cultivated in remote locations and frequently on public lands. Data provided by the DCE/SP (Table 4) shows that in 2009, there were 9,980,038 plants eradicated in outdoor cannabis cultivation areas in the United States. Marijuana is illicitly grown in all states. Major domestic outdoor cannabis cultivation areas were found in California, Kentucky, Tennessee and Hawaii. Significant quantities of marijuana were also eradicated from indoor cultivation operations. There were 414,604 indoor plants eradicated in 2009 compared to 217,105 eradicated in 2000. As indoor cultivation is generally associated with plants that have higher concentrations of $\Delta^9$-THC, the larger numbers of indoor grow facilities may be impacting the higher average $\Delta^9$-THC concentrations of seized materials.

TABLE 4—DOMESTIC CANNABIS ERADICATION, OUTDOOR AND INDOOR PLANTS SEIZED, 2000–2009

[Source: Domestic Cannabis Eradication/Suppression Program]

| | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 |
|---|---|---|---|---|---|---|---|---|---|---|
| Outdoor | 2,597,798 | 3,068,632 | 3,128,800 | 3,427,923 | 2,996,144 | 3,938,151 | 4,830,766 | 6,599,599 | 7,562,322 | 9,980,038 |
| Indoor | 217,105 | 236,128 | 213,040 | 223,183 | 203,896 | 270,935 | 400,892 | 434,728 | 450,986 | 414,604 |
| Total | 2,814,903 | 3,304,760 | 3,341,840 | 3,651,106 | 3,200,040 | 4,209,086 | 5,231,658 | 7,034,327 | 8,013,308 | 10,394,642 |

The recent statistics from these various surveys and databases show that marijuana continues to be the most commonly used illicit drug, with considerable rates of heavy abuse and dependence. They also show that marijuana is the most readily available illicit drug in the United States.

The petitioner states that, "The abuse potential of cannabis is insufficient to justify the prohibition of medical use." The petitioner also states that, "[s]everal studies demonstrate that abuse rates for cannabis are lower than rates for other common drugs." (Exh. C, Section IV(16), pg. 92).

DHHS states, to the contrary, "the large number of individuals using marijuana on a regular basis, its widespread use, and the vast amount of marijuana that is available for illicit use are indicative of the high abuse potential for marijuana." Indeed, the data presented in this section shows that marijuana has a high potential for abuse as determined using the indicators identified in the CSA's legislative history. Both clinical and preclinical studies have demonstrated that marijuana and its principal psychoactive constituent $\Delta^9$-THC possess the attributes associated with drugs of abuse. They function as positive reinforcers and as discriminative stimuli to maintain drug-seeking behavior.

In addition, marijuana is the most highly abused and trafficked illicit substance in the United States. Chronic abuse has resulted in a considerable number of individuals seeking substance abuse treatment according to national databases such as TEDS. Abuse of marijuana is associated with significant public health and safety risks that are described under factors 2, 6 and 7.

The issue of whether marijuana has a currently accepted medical use is discussed under Factor 3.

The petitioner claims that, "[...]widespread use of marijuana without dependency supports the argument that marijuana is safe for use under medical supervision." (Exh. C, Section IV(15), pg. 87).

Petitioner's claim of widespread use without dependency is not supported by abuse-related data. In particular, this claim disregards the high numbers of admissions to treatment facilities for marijuana abuse. Indeed, TEDS admissions for primary abuse of marijuana/hashish accounted for roughly 17 percent of all treatment admissions in 2008. In 2008, 2,016,256 people were admitted to drug and alcohol treatment in the United States and 346,679 of those admissions were for marijuana/hashish abuse. These drug treatment numbers are not consistent with this claim. Marijuana is not safe for use under medical supervision, and this point is addressed further in Factor 3.

The petitioner also claims that, "Data on both drug treatment and emergency room admissions also distinguishes the abuse potential of marijuana from that of other drugs and establishes its relative abuse potential as lower than schedule I drugs such as heroin and schedule II drugs such as cocaine." (Exh. C, Section IV(17), pg. 99). The petitioner then presents data from TEDS in 1998, in which a larger proportion of all marijuana treatment admissions are referred to by the criminal justice system (54 percent), compared to much smaller percentages for heroin and cocaine. The petitioner argues that the abuse potential of these other drugs is more severe such that addicts seek treatment on their own or through persuasion of their associates, and claims that this difference establishes marijuana's relative abuse potential as lower than the other drugs.

Petitioner's claim is not supported by an examination of the absolute numbers of admissions for treatment for each drug discussed. Regardless of proportions of referrals from the criminal justice systems, the absolute numbers of admissions for treatment for marijuana, heroin, or cocaine dependence are very high. Furthermore, data from TEDS in 2007 (SAMHSA, 2009) show that both primary marijuana and methamphetamine/amphetamine admissions had the largest proportion of admissions referred through the criminal justice system (57 percent each), followed by PCP (54 percent). Both methamphetamine/amphetamine and PCP have very high potential for abuse (Lile, 2006; Crider, 1986). Accordingly, this illustrates that it is not possible to establish or predict relative abuse potentials from the ranking of proportions of treatment admissions referred by the criminal justice system.

## FACTOR 2: SCIENTIFIC EVIDENCE OF THE DRUG'S PHARMACOLOGICAL EFFECTS, IF KNOWN

DHHS states that there are abundant scientific data available on the neurochemistry, toxicology, and pharmacology of marijuana. Following is a summary of the current scientific understanding of the endogenous cannabinoid system and of marijuana's pharmacological effects, including its effects on the cardiovascular, respiratory, and immune systems, as well as its effects on mental health and cognitive function and the effect of prenatal exposure to marijuana.

### Neurochemistry of the Psychoactive Constituents of Marijuana

DHHS states that of 483 natural constituents identified in marijuana, 66 are classified as cannabinoids (Ross and El Sohly, 1995). Cannabinoids are not known to exist in plants other than marijuana and most of the cannabinoid compounds have been identified chemically. The activity of marijuana is largely attributed to $\Delta^9$-THC (Wachtel *et al.*, 2002).

DEA notes that $\Delta^9$-THC and delta-8-tetrahydrocannabinol ($\Delta^8$-THC) are the only known compounds in the cannabis plant which show all the psychoactive effects of marijuana. $\Delta^9$-THC is more abundant than $\Delta^8$-THC and $\Delta^9$-THC concentrations vary within portions of the cannabis plant (Hanus and Subivá, 1989; Hanus *et al.*, 1975). 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 mechanism of action of $\Delta^9$-THC was verified with the cloning of cannabinoid receptors, first from rat brain tissue (Matsuda *et al.*, 1990) and then from human brain tissue (Gerard *et al.*, 1991). Two cannabinoid receptors have been identified and characterized, $CB_1$ and $CB_2$ (Piomelli, 2005). Autoradiographic studies have provided information on the distribution of $CB_1$ and $CB_2$ receptors. High densities of $CB_1$ receptors are found in the basal ganglia, hippocampus, and cerebellum of the brain (Howlett *et al.*, 2004; Herkenham *et al.*, 1990; Herkenham, 1992). These brain regions are associated with movement coordination and cognition and the location of $CB_1$ receptors in these areas may explain cannabinoid interference with these functions. Although $CB_1$ receptors are predominantly expressed in the brain, they have also been detected in the immune system (Bouaboula *et al.*, 1993). $CB_2$ receptors are primarily located in B lymphocytes and natural killer cells of the immune system and it is believed that this receptor is responsible for mediating immunological effects of cannabinoids (Galiegue *et al.*, 1995). Recently, however, $CB_2$ receptors have been localized in the brain, primarily in the cerebellum and hippocampus (Gong *et al.*, 2006).

Cannabinoid receptors are linked to an inhibitory G-protein (Breivogel and Childers, 2000). When the receptor is activated, adenylate cyclase activity is inhibited, preventing the conversion of adenosine triphosphate (ATP) to the second messenger cyclic adenosine monophosphate (cAMP). Other examples of inhibitory-coupled receptors include opioid, muscarinic cholinergic, alpha$_2$-adrenoreceptors, dopamine and serotonin receptors. However, several studies also suggest a link to stimulatory G-proteins, through which activation of $CB_1$ stimulates adenylate cyclase activity (Glass and Felder, 1997; Maneuf and Brotchie, 1997; Felder *et al.*, 1998).

Activation of $CB_1$ receptors inhibits N-and P/Q-type calcium channels and activate inwardly rectifying potassium channels (Mackie *et al.*, 1995; Twitchell *et al.*, 1997). Inhibition of N-type calcium channels decreases neurotransmitter release from a number of tissues and may be the mechanism by which cannabinoids inhibit acetylcholine, norepinephrine, and glutamate release from specific areas of the brain. These effects on G protein-mediated pathways and on calcium and potassium channels may represent potential cellular mechanisms underlying the antinociceptive and psychoactive effects of cannabinoids (Ameri, 1999).

Delta$^9$-THC displays similar affinity for both cannabinoid receptors but behaves as a weak agonist at $CB_2$ receptors, based on inhibition of adenylate cyclase. The identification of synthetic cannabinoid ligands that selectively bind to $CB_2$ receptors but do not have the typical $\Delta^9$-THC-like psychoactive properties, along with the respective anatomical distribution of the two receptor subtypes suggests that the psychoactive effects of cannabinoids are mediated through the activation of $CB_1$ receptors (Hanus *et al.*, 1999). Naturally occurring cannabinoids and synthetic cannabinoid agonists (such as WIN-55,212-2 and CP-55,940) produce hypothermia, analgesia, hypoactivity, and catalepsy in addition to their psychoactive effects.

In 2000, two endogenous cannabinoid receptor agonists were discovered, anandamide and arachidonyl glycerol (2-AG). Anandamide is a low efficacy agonist (Breivogel and Childers, 2000) and 2-AG is a highly efficacious agonist (Gonsiorek *et al.*, 2000). These endogenous ligands are present in both central and peripheral tissues. The physiological role of these endogenous ligands is an active area of research (Martin *et al.*, 1999).

In summary, two receptors have been cloned, $CB_1$ (found in the central nervous system) and CB2 (predominantly found in the periphery), that bind $\Delta^9$-THC and other cannabinoids. Activation of these inhibitory G-protein-coupled receptors inhibits calcium channels and adenylate cyclase. Endogenous cannabinoid agonists have been identified, anandamide and arachidonyl glycerol (2-AG).

### Pharmacological Effects of Marijuana

Marijuana produces a number of central nervous system effects. Many of these effects are directly related to the abuse potential of marijuana, and are discussed in Factor 1. Other effects are discussed herein.

### Cardiovascular and Autonomic Effects

DHHS states that acute use of marijuana causes an increase in heart rate (tachycardia) and may cause a modest increase in blood pressure as well (Capriotti *et al.*, 1988; Benowitz and Jones, 1975). Conversely, chronic exposure to marijuana will produce a decrease in heart rate (bradycardia) and decrease of blood pressure. In heavy smokers of marijuana, the degree of increased heart rate is diminished due to the development of tolerance (Jones, 2002 and Sidney, 2002). These effects are thought to be mediated through peripherally located, presynaptic $CB_1$ receptor inhibition of norepinephrine release with possible direct activation of vascular cannabinoid receptors (Wagner *et al.*, 1998).

DHHS cites a review (Jones, 2002) of studies showing that smoked marijuana causes orthostatic hypotension (sympathetic insufficiency, a sudden drop in blood pressure upon standing up) often accompanied by dizziness. DHHS states that tolerance can develop to this effect.

Marijuana smoking by older patients, particularly those with some degree of coronary artery or cerebrovascular disease, poses risks related to increased cardiac work, increased catecholamines, carboxyhemoglobin, and postural hypotension (Benowitz and Jones, 1981; Hollister, 1988).

DEA further notes studies in which marijuana has been administered under controlled conditions to marijuana-experienced users that showed that marijuana causes a substantial increase, compared to placebo, in heart rate (tachycardia) ranging from 20 percent to 100 percent above baseline. This effect was seen as usually greatest starting during the 10 minutes or so it takes to smoke a marijuana cigarette and lasting 2 to 3 hours (reviewed in Jones *et al.*, 2002).

DEA also notes a randomized, double-blind, placebo-controlled study by Mathew and colleagues (2003) that examined pulse rate, blood pressure (BP), and plasma $\Delta^9$-THC levels during reclining and standing for 10 minutes before and after smoking one marijuana cigarette (3.55 percent $\Delta^9$-THC) by twenty-nine volunteers. Marijuana induced postural dizziness, with 28 percent of subjects reporting severe symptoms. Intoxication and dizziness peaked immediately after drug intake. The severe dizziness group showed the most marked postural drop in blood pressure and showed a drop in pulse rate after an initial increase during standing.

**Respiratory Effects**

Both acute and chronic respiratory effects are associated with marijuana smoking.

DHHS states that acute exposure to marijuana produces transient bronchodilation (Gong *et al.*, 1984). DHHS states that long-term use of smoked marijuana can lead to increased frequency of chronic cough, increased sputum, large airway obstruction, as well as cellular inflammatory histopathological abnormalities in bronchial epithelium (Adams and Martin, 1996; Hollister, 1986).

DEA notes a study showing that both smoked marijuana and oral $\Delta^9$-THC increases specific airway conductance in asthmatic subjects (Tashkin *et al.*, 1974). In addition, other studies have suggested that chronic marijuana smoking is also associated with increased incidence of emphysema and asthma (Tashkin *et al.*, 1987).

DHHS states that the evidence that marijuana may lead to cancer is inconsistent, with some studies suggesting a positive correlation while others do not. DHHS cited a large clinical study with 1,650 subjects in which no positive correlation was found between marijuana use and lung cancer (Tashkin *et al.*, 2006). This finding held true regardless of the extent of marijuana use when both tobacco use and other potential confounding factors were controlled. DHHS also cites other studies reporting lung cancer occurrences in young marijuana users with no history of tobacco smoking (Fung *et al.*, 1999), and suggesting a dose-dependent effect of marijuana on the risk of head and neck cancer (Zhang *et al.*, 1999).

DEA notes the publication of a more recent case–control study of lung cancer in adults under 55 years of age, conducted in New Zealand by Aldington and colleagues (2008). Interviewer-administered questionnaires were used to assess possible risk factors, including cannabis use. In total, 79 cases of lung cancer and 324 controls were included in the study. The risk of lung cancer increased 8 percent (95 percent confidence interval (CI) 2–15) for each joint-year of cannabis smoking (one joint-year being equivalent to one joint per day for a year), after adjustment for confounding variables including cigarette smoking; it went up 7 percent (95 percent CI 5–9) for each pack-year of cigarette smoking (one pack-year being equivalent to one pack per day for a year), after adjustment for confounding variables including cannabis smoking. Thus, a major differential risk between cannabis and cigarette smoking was observed, with one joint of cannabis being similar to 20 cigarettes for risk of lung cancer. Users reporting over 10.5 joint-years of exposure had a significantly increased risk of developing lung cancer (relative risk 5.7 (95 percent CI 1.5–21.6)) after adjustment for confounding variables including cigarette smoking. DEA notes that the authors of this study concluded from their results that long-term cannabis use increases the risk of lung cancer in young adults.

Some studies discuss marijuana smoke and tobacco smoke. DHHS states that chronic exposure to marijuana smoke is considered to be comparable to tobacco smoke with respect to increased risk of cancer and lung damage. DEA notes studies showing that marijuana smoke contains several of the same carcinogens and co-carcinogens as tobacco smoke and suggesting that pre-cancerous lesions in bronchial epithelium also seem to be caused by long-term marijuana smoking (Roth *et al.*, 1998).

In summary, studies are still needed to clarify the impact of marijuana on the risk of developing lung cancer as well as head and neck cancer. DHHS states that the evidence that marijuana may lead to cancer is inconsistent, with some studies suggesting a positive correlation while others do not.

**Endocrine Effects**

DHHS states that $\Delta^9$-THC reduces binding of the corticosteroid dexamethasone in hippocampal tissue from adrenalectomized rats and acute $\Delta^9$-THC releases corticosterone, with tolerance developing to this effect with chronic administration (Eldridge *et al.*, 1991). These data suggest that $\Delta^9$-THC may interact with the glucocorticoid receptor system.

DHHS states that experimental administration of marijuana to humans does not consistently alter the endocrine system. In an early study, four male subjects administered smoked marijuana showed a significant depression in luteinizing hormone and a significant increase in cortisol (Cone *et al.*, 1986). However, later studies in male subjects receiving smoked $\Delta^9$-THC (18 mg/marijuana cigarette) or oral $\Delta^9$-THC (10 mg t.i.d. for 3 days) showed no changes in plasma prolactin, ACTH, cortisol, luteinizing hormone or testosterone levels (Dax *et al.*, 1989). Similarly, a study with 93 males and 56 female subjects showed that chronic marijuana use did not significantly alter concentrations of testosterone, luteinizing hormone, follicle stimulating hormone, prolactin or cortisol (Block *et al.*, 1991).

DHHS cites a study (Sarfaraz *et al.*, 2005) which showed that the cannabinoid agonist WIN 55,212-2 induces apoptosis in prostate cancer cells growth and decreases expression of androgen receptors. DHHS states that this data suggests a potential therapeutic value for cannabinoid agonists in the treatment of prostate cancer, an androgen-stimulated type of carcinoma.

In summary, while animal studies have suggested that cannabinoids can alter multiple hormonal systems, the effects in humans, in particular the consequences of long-term marijuana abuse, remain unclear.

**Immune System Effects**

DHHS states that cannabinoids alter immune function but that there can be differences between the effects of synthetic, natural, and endogenous cannabinoids (Croxford and Yamamura, 2005).

DHHS cites a study by Roth *et al.* (2005) that examined the effect of $\Delta^9$-THC exposure on immune function and response to HIV infection in immunodeficient mice that were implanted with human blood cells infected with HIV. The study shows that exposure to $\Delta^9$-THC *in vivo* suppresses immune function, increases HIV co-receptor expression and acts as a cofactor to enhance HIV replication. DEA notes that the authors of this study state that their results suggest a dynamic interaction between $\Delta^9$-THC, immunity, and the pathogenesis of HIV and support epidemiologic studies that have identified marijuana use as a risk factor for HIV infection and the progression of AIDS. However, DHHS discusses a recent study by Abrams *et al.* (2003) that investigated the effect of marijuana on immunological functioning in 67 AIDS patients who were taking protease inhibitors. Subjects received one of three treatments, three times a day: smoked marijuana cigarette containing 3.95 percent $\Delta^9$-THC; oral tablet containing $\Delta^9$-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.

DEA notes a review suggesting that $\Delta^9$-THC and cannabinoids decrease resistance to microbial infections in experimental animal models and *in vitro* (see review by Cabral and Staab, 2005). Various studies have been conducted in drug-abusing human subjects, experimental animals exposed to marijuana smoke or injected with cannabinoids, and in *in vitro* models using immune cell cultures treated with various cannabinoids. DEA notes that for the most part, these studies suggest that cannabinoids modulate the function of various cells of the human immune system, including T- and B-

lymphocytes as well as natural killer (NK) cells and macrophages. Macrophages engulf and destroy foreign matter, NK cells target cells (e.g., cancerous cells) and destroy them, B-lymphocytes produce antibodies against infective organisms, and T-lymphocytes kill cells or trigger the activity of other cells of the immune system.

In addition to studies examining cannabinoid effects on immune cell function, DEA also notes other reports which have documented that cannabinoids modulate resistance to various infectious agents. Viruses such as herpes simplex virus and murine retrovirus have been studied as well as bacterial agents such as members of the genera Staphylococcus, Listeria, Treponema, and Legionella. These studies suggest that cannabinoids modulate host resistance, especially the secondary immune response (reviewed in Cabral and Dove-Pettit, 1998).

Finally, DEA notes a review suggesting that cannabinoids modulate the production and function of cytokines as well as modulate the activity of network cells such as macrophages and T helper cells. Cytokines are the chemicals produced by cells of the immune system in order to communicate and orchestrate the attack. Binding to specific receptors on target cells, cytokines recruit many other cells and substances to the field of action. Cytokines also encourage cell growth, promote cell activation, direct cellular traffic, and destroy target cells (see review by Klein *et al.*, 2000).

In summary, as DHHS states, cannabinoids alter immune function, but there can be differences between the effects of synthetic, natural, and endogenous cannabinoids. While there is a large body of evidence to suggest that $\Delta^9$-THC alters immune function, research is still needed to clarify the effects of cannabinoids and marijuana on the immune system in humans, in particular the risks posed by smoked marijuana in immunocompromized individuals.

**Association with Psychosis**

The term psychosis is generally used in research as a generic description of severe mental illnesses characterized by the presence of delusions, hallucinations and other associated cognitive and behavioral impairments. Psychosis is measured either by using standardized diagnostic criteria for psychotic conditions such as schizophrenia or by using validated scales that rank the level of psychotic symptoms from none to severe (Fergusson *et al.*, 2006).

DHHS states that extensive research has been conducted recently to investigate whether exposure to marijuana is associated with schizophrenia or other psychoses. DHHS states that, at the time of their review, the data does not suggest a causative link between marijuana use and the development of psychosis.

DHHS discusses an early epidemiological study conducted by Andreasson and colleagues (1987), which examined the link between psychosis and marijuana use. In this study, 45,000 18- and 19-year-old male Swedish subjects provided detailed information on their drug-taking history. The incidence of schizophrenia was then recorded over the next 15 years. Those individuals who claimed, on admission, to have taken marijuana on more than 50 occasions were six times more likely to be diagnosed with schizophrenia in the following 15 years than those who had never consumed the drug. When confounding factors were taken into account, the risk of developing schizophrenia remained statistically significant. The authors concluded that marijuana users who are vulnerable to developing psychoses are at the greatest risk for schizophrenia. DHHS states that therefore marijuana per se does not appear to induce schizophrenia in the majority of individuals who try or continue to use the drug.

DHHS discusses another large longitudinal study in which the prevalence of schizophrenia was modeled against marijuana use across birth cohorts in Australia from 1940 to 1979 (Degenhardt *et al.*, 2003). The authors found that marijuana use may precipitate disorders in vulnerable individuals and worsen the course of the disorder among those that have already developed it. They did not find any causal relationship between marijuana use and increased incidence of schizophrenia.

DEA notes that Degenhardt and colleagues (2003) acknowledged that several environmental risk factors for schizophrenia had been reduced (i.e., poor maternal nutrition, infectious disease and poor antenatal and prenatal care) and that the diagnostic criteria for schizophrenia had changed over the span of this study making the classification of schizophrenia more rigorous. These confounders could reduce the reported prevalence of schizophrenia.

DHHS also discusses several longitudinal studies that found a dose-response relationship between marijuana use and an increasing risk of psychosis among those who are vulnerable to developing psychosis (Fergusson *et al.*, 2005; van Os *et al.*, 2002).

DEA notes several longitudinal studies (Arseneault *et al.*, 2002, Caspi *et al.*, 2005; Henquet *et al.*, 2005) that found increased rates of psychosis or psychotic symptoms in people using cannabis. Finally, DEA notes some studies that observe that individuals with psychotic disorders have higher rates of cannabis use compared to the general population (Regier *et al.*, 1990; Green *et al.*, 2005).

DEA also notes that, more recently, Moore and colleagues (2007) performed a meta-analysis of the longitudinal studies on the link between cannabis use and subsequent psychotic symptoms. Authors observed that there was an increased risk of any psychotic outcome in individuals who had ever used cannabis (pooled adjusted odds ratio=1.41, 95 percent CI 1.20–1.65). Furthermore, findings were consistent with a dose-response effect, with greater risk in people who used cannabis most frequently (2.09, 1.54–2.84). The authors concluded that their results support the view that cannabis increases risk of psychotic outcomes independently of confounding and transient intoxication effects.

DEA also notes another more recent study examining the association between marijuana use and psychosis-related outcome in pairs of young adult siblings in Brisbane, Australia (McGrath *et al.*, 2010). This study found a dose-response relationship where the longer the duration of time since the first cannabis use, the higher the risk of psychosis-related outcome. Those patients with early-onset psychotic symptoms were also likely to report early marijuana use. Authors suggest that their results support the hypothesis that early cannabis use is a risk-modifying factor for psychosis-related outcomes in young adults.

**Cognitive Effects**

DHHS states that acute administration of smoked marijuana impairs performance on tests of learning, associative processes, and psychomotor behavior (Block *et al.*, 1992; Heishman *et al.*, 1990). Marijuana may therefore considerably interfere with an individual's ability to learn in a classroom or to operate motor vehicles. DHHS cites a study conducted by Kurzthalar and colleagues (1999) with human volunteers, in which the administration of 290 µg/kg of $\Delta^9$-THC in a smoked cigarette resulted in impaired perceptual motor speed and accuracy, skills of paramount importance for safe driving. Similarly, administration of 3.95 percent $\Delta^9$-THC in a smoked cigarette increased disequilibrium measures, as well as the latency in a task of simulated vehicle braking (Liguori *et al.*, 1998).

DHHS states that the effects of marijuana may not be fully resolved until at least one day after the acute psychoactive effects have subsided, following repeated administration. Heishman and colleagues (1988) showed that impairment on memory tasks persists for 24 hours after smoking marijuana cigarettes containing 2.57 percent $\Delta^9$-THC. However, Fant and colleagues (1998) showed minimal residual alterations in subjective or performance measures the day after subjects were exposed to 1.8 percent or 3.6 percent smoked $\Delta^9$-THC.

DHHS discussed a study by Lyons and colleagues (2004) on the neuropsychological consequences of regular marijuana use in fifty-four monozygotic male twin pairs, with one subject being a regular user and its co-twin a non-user, and neither twin having used any other illicit drug regularly. Marijuana-using twins significantly differed from their non-using co-twins on the general intelligence domain. However, only one significant difference was noted between marijuana-using twins and their non-using co-twins on measures of cognitive functioning. Authors of the study proposed that the results indicate an absence of any marked long-term residual effects of marijuana use on cognitive abilities. This conclusion is similar to the results found by Lyketsos and colleagues (1999), who investigated the possible adverse effects of cannabis use on cognitive decline after 12 years in persons under 65 years of age. There were no significant differences in cognitive decline between heavy users, light users, and nonusers of cannabis. The authors conclude that over long time periods, in persons under age 65 years, cognitive decline occurs in all age groups. This decline is closely associated with aging and educational level but does not appear to be associated with cannabis use.

DEA notes that while Lyketsos and colleagues (1999) propose that their results

provide strong evidence of the absence of a long term residual effect of cannabis use on cognition, they also acknowledge a number of limitations to their study. Notably, authors remark that it is possible that some cannabis users in the study may have used cannabis on the day the test was administered. Given the acute effects on cannabis on cognition, this would have tended to reduce their test score on that day. This may have adversely affected accurate measurement of test score changes over time in cannabis users. The authors also noted, as another important limitation, that the test used is not intended for the purpose for which it was used in this study and is not a very sensitive measure of cognitive decline, even though it specifically tests memory and attention. Thus, small or subtle effects of cannabis use on cognition or psychomotor speed may have been missed.

DHHS also discussed a study by Solowij and colleagues (2002) which examined the effects of duration of cannabis use on specific areas of cognitive functioning among users seeking treatment for cannabis dependence. They compared 102 near-daily cannabis users (51 long-term users: mean, 23.9 years of use; 51 shorter-term users: mean, 10.2 years of use) with 33 nonuser controls. They collected measures from nine standard neuropsychological tests that assessed attention, memory, and executive functioning, and that were administered prior to entry to a treatment program and following a median 17-hour abstinence. Authors found that long-term cannabis users performed significantly less well than shorter-term users and controls on tests of memory and attention. Long-term users showed impaired learning, retention, and retrieval compared with controls. Both user groups performed poorly on a time estimation task. Performance measures often correlated significantly with the duration of cannabis use, being worse with increasing years of use, but were unrelated to withdrawal symptoms and persisted after controlling for recent cannabis use and other drug use. Authors of this study state that their results support the hypothesis that long-term heavy cannabis users show impairments in memory and attention that endure beyond the period of intoxication and worsen with increasing years of regular cannabis use.

DHHS cited a study by Messinis and colleagues (2006) which examined neurophysiological functioning for heavy, frequent cannabis users. The study compared 20 long-term (LT) and 20 shorter-term (ST) heavy, frequent cannabis users after abstinence for at least 24 hours prior to testing with 24 non-using controls. LT users performed significantly worse on verbal memory and psychomotor speed. LT and ST users had a higher proportion of deficits on verbal fluency, verbal memory, attention and psychomotor speed. Authors conclude from their study that specific cognitive domains appear to deteriorate with increasing years of heavy frequent cannabis use.

DHHS discussed a study by Pope and colleagues (2003) which reported no differences in neuropsychological performance in early- or late-onset users compared to non-using controls, after adjustment for intelligence quotient (IQ). In another cohort of chronic, heavy marijuana users, some deficits were observed on memory tests up to a week following supervised abstinence but these effects disappeared by day 28 of abstinence (Pope *et al.*, 2002). The authors concluded that "cannabis-associated cognitive deficits are reversible and related to recent cannabis exposure rather than irreversible and related to cumulative lifetime use." Conversely, DHHS notes that other investigators have reported persistent neuropsychological deficits in memory, executive functioning, psychomotor speed, and manual dexterity in heavy marijuana smokers who had been abstinent for 28 days (Bolla *et al.*, 2002). Furthermore, when dividing the group into light, middle, and heavy user groups, Bolla and colleagues (2002) found that the heavy user group performed significantly below the light user group on 5 of 35 measures. A follow-up study of heavy marijuana users noted decision-making deficits after 25 days of abstinence (Bolla *et al.*, 2005). When IQ was contrasted in adolescents 9–12 years of age and at 17–20 years of age, current heavy marijuana users showed a 4-point reduction in IQ in later adolescence compared to those who did not use marijuana (Fried *et al.*, 2002).

DHHS states that age of first use may be a critical factor in persistent impairment 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 16 (Ehrenreich *et al.*, 1999). DHHS's document noted that Kandel and Chen (2000) assert that 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.

DEA notes an additional recent study that indicates that because neuromaturation continues through adolescence, results on the long-lasting cognitive effects of marijuana use in adults cannot necessarily generalize to adolescent marijuana users. Medina and colleagues (2007) examined neuropsychological functioning in 31 adolescent abstinent marijuana users, after a period of abstinence from marijuana of 23 to 28 days, and in 34 demographically similar control adolescents, all 16–18 years of age. After controlling for lifetime alcohol use and depressive symptoms, adolescent marijuana users demonstrated slower psychomotor speed (p .05), and poorer complex attention (p .04), story memory (p .04), and planning and sequencing ability (p .001) compared with nonusers. The number of lifetime marijuana use episodes was associated with poorer cognitive function, even after controlling for lifetime alcohol use. The general pattern of results suggested that, even after a month of monitored abstinence, adolescent marijuana users demonstrate subtle neuropsychological deficits compared with nonusers. The authors of this study suggest that frequent marijuana use during adolescence may negatively influence neuromaturation and cognitive development.

In summary, acute administration of marijuana impairs performance on tests of learning, associative processes, and psychomotor behavior. The effects of chronic marijuana use have also been studied. While a few studies did not observe strong persistent neurocognitive consequences of long-term cannabis use (Lyketsos *et al.*, 1999; Lyons *et al.*, 2004), others provide support for the existence of persistent consequences (Bolla *et al.*, 2002, 2005). The cognitive impairments that are observed 12 hours to seven days after marijuana use (Messinis *et al.*, 2006; Solowij *et al.*, 2002; Harrison *et al.*, 2002), and that persist beyond behaviorally detectable intoxication, are noteworthy and may have significant consequences on workplace performance and safety, academic achievement, and automotive safety. In addition, adolescents may be particularly vulnerable to the long-lasting deleterious effects of marijuana on cognition. The overall significant effect on general intelligence as measured by IQ should also not be overlooked.

**Behavioral Effects of Prenatal Exposure**

The impact of *in utero* marijuana exposure on performance in a series of cognitive tasks has been studied in children of various ages. DHHS concludes in its analysis of the presently examined petition that since many marijuana users have abused other drugs, it is difficult to determine the specific impact of marijuana on prenatal exposure. Fried and Watkinson (1990) found that four year old children of heavy marijuana users have deficits in memory and verbal measures. Maternal marijuana use is predictive of poorer performance on abstract/visual reasoning tasks of three year old children (Griffith *et al.*, 1994) and an increase in omission errors on a vigilance task of six year olds (Fried *et al.*, 1992). When the effect of prenatal exposure in nine to 12 year old children is analyzed, in utero exposure to marijuana is negatively associated with executive function tasks that require impulse control, visual analysis, and hypothesis testing (Fried *et al.*, 1998).

DEA notes studies showing that $\Delta^9$-THC passes the placental barrier (Idanpaan-Heikkila *et al.*, 1969) and that fetal blood concentrations are at least equal to those found in the mother's blood (Grotenhermen, 2003).

In summary, smoked marijuana exerts a number of cardiovascular and respiratory effects, both acutely and chronically. Marijuana's main psychoactive ingredient $\Delta^9$-THC alters immune function. The cognitive impairments caused by marijuana use that persist beyond behaviorally detectable intoxication may have significant consequences on workplace performance and safety, academic achievement, and automotive safety, and adolescents may be particularly vulnerable to marijuana's cognitive effects. Prenatal exposure to marijuana was linked to children's poorer performance in a number of cognitive tests.

**FACTOR 3: THE STATE OF THE CURRENT SCIENTIFIC KNOWLEDGE REGARDING THE DRUG OR SUBSTANCE**

DHHS states that marijuana is a mixture of the dried leaves and flowering tops of the cannabis plant (Agurell *et al.*, 1984; Graham,

1976; Mechoulam, 1973). These portions of the plant have the highest levels of $\Delta^9$-THC, the primary psychoactive ingredient in marijuana. The most potent product (i.e., that having the highest percentage of $\Delta^9$-THC) of dried material is sinsemilla, derived from the unpollinated flowering tops of the female cannabis plant. Generally, this potent marijuana product is associated with indoor grow sites and may have a $\Delta^9$-THC content of 15 to 20 percent or more. Other, less common forms of marijuana found on the illicit market are hashish and hashish oil. Hashish is a $\Delta^9$-THC-rich resinous material of the cannabis plant which is dried and compressed into a variety of forms (balls, cakes or sticks). Dried pieces are generally broken off and smoked. $\Delta^9$-THC content is usually about five percent. The Middle East, North Africa and Pakistan/Afghanistan are the main sources of hashish. Hashish oil is produced by extracting the cannabinoids from plant material with a solvent. Hashish oil is a light to dark brown viscous liquid with a $\Delta^9$-THC content of about 15 percent. The oil is often sprinkled on cigarettes, allowed to dry, and then smoked.

**Chemistry**

DHHS states that some 483 natural constituents have been identified in marijuana, including 66 compounds that are classified as cannabinoids (Ross and El Sohly, 1995). Cannabinoids are not known to exist in plants other than marijuana, and most naturally occurring cannabinoids have been identified chemically. The psychoactive properties of cannabis are attributed to one or two of the major cannabinoid substances, namely delta-9- tetrahydrocannabinol ($\Delta^9$-THC) and delta-8-tetrahydrocannabinol ($\Delta^8$-THC). Other natural cannabinoids, such as cannabidiol (CBD) and cannabinol (CBN), have been characterized. CBD does not possess $\Delta^9$-THC-like psychoactivity. Its pharmacological properties appear to include anticonvulsant, anxiolytic and sedative properties (Agurell *et al.*, 1984, 1986; Hollister, 1986).

DHHS states that $\Delta^9$-THC is an optically active resinous substance, extremely lipid soluble, and insoluble in water. Chemically, $\Delta^9$-THC 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).

DEA notes a review of the contaminants and adulterants that can be found in marijuana (McPartland, 2002). In particular, DEA notes that many studies have reported contamination of both illicit and NIDA-grown marijuana with microbial contaminants, bacterial or fungal (McLaren *et al.*, 2008; McPartland, 1994, 2002; Ungerleider *et al.*, 1982; Taylor *et al.*, 1982; Kurup *et al.*, 1983). Other microbial contaminants include Klebsiella pneumoniae, salmonella enteritidis, and group D Streptococcus (Ungerlerder *et al.*, 1982; Kagen *et al.*, 1983; Taylor *et al.*, 1982). DEA notes that a review by McLaren and colleagues (2008) discusses studies showing that heavy metals present in soil may also contaminate cannabis, and states that these contaminants have the potential to harm the user without harming the plant. Other sources of contaminants discussed by McLaren and colleagues (2008) include growth enhancers and pest control products related to marijuana cultivation and storage.

**Human Pharmacokinetics**

DHHS states that marijuana is generally smoked as a cigarette (weighing between 0.5 and 1.0 gm; Jones, 1980) or in a pipe. It can also be taken orally in foods or as extracts of plant material in ethanol or other solvents. The absorption, metabolism, and pharmacokinetic profile of $\Delta^9$-THC (and other cannabinoids) in marijuana or other drug products containing $\Delta^9$-THC vary with 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 is absorbed within seconds. The psychoactive effects of marijuana occur immediately following absorption, with mental and behavioral effects measurable up for to six hours after absorption (Grotenhermen, 2003; Hollister, 1986, 1988). $\Delta^9$-THC is delivered to the brain rapidly and efficiently as would be expected of a highly lipid-soluble drug.

The petitioner provided a discussion of new, or less common, routes and methods of administration being currently explored (pg. 57, line 1). These include vaporization for the inhalation route, as well as rectal, sublingual, and transdermal routes.

DEA notes that respiratory effects are only part of the harmful health effects of prolonged marijuana exposure, as described further under factor 2 of this document. DEA also notes that at this time, the majority of studies exploring the potential therapeutic uses of marijuana use smoked marijuana, and the pharmacokinetics and bioavailability from routes of administration other than smoked and oral are not well-known.

The pharmacokinetics of smoked and orally ingested marijuana are thoroughly reviewed in DHHS's review document.

**Medical Utility**

The petition filed by the Coalition to Reschedule Cannabis (Marijuana) aims to repeal the rule placing marijuana in schedule I of the CSA, based in part on the proposition that marijuana has an accepted medical use in the United States. However DHHS has concluded in its 2006 analysis that marijuana has no accepted medical use in treatment in the United States. Following is a discussion of the petitioner's specific points and a presentation of DHHS's evaluation and recommendation on the question of accepted medical use for marijuana.

The petitioner states (pg. 48, line 2), "Results from clinical research demonstrated that both dronabinol and whole plant cannabis can offer a safe and effective treatment for the following illnesses: muscle spasm in multiple sclerosis, Tourette syndrome, chronic pain, nausea and vomiting in HIV/AIDS and cancer chemotherapy, loss of appetite from cancer, hyperactivity of the bladder in patients with multiple sclerosis and spinal cord injury, and dyskinesia caused by levodopa in Parkinson's disease."

To support its claim that marijuana has an accepted medical use in the United States, the petitioner listed supporting evidence that included the following:

- Evidence from clinical research and reviews of earlier clinical research (Exh. C, Section I (4, 6), pg. 29)
- Acceptance of the medical use of marijuana by eight states since 1996 and state officials in these states establishing that marijuana has an accepted medical use in the United States (Exh. C, Section I (1), pg. 13)
- Increased recognition by health care professionals and the medical community, including the Institute of Medicine (IOM) (Exh. C, Section I (2), pg. 15)
- Patients' experience in which they reported benefits from smoking marijuana (Exh. C, Section I (3), pg. 22)
- *Evidence from clinical research (Exh. C, Section I (4, 6), pg. 29)*

DHHS states that a new drug application (NDA) for marijuana has not been submitted to the FDA for any indication and thus no medicinal product containing botanical cannabis has been approved for marketing. Only small clinical studies published in the current medical literature demonstrate that research with marijuana is being conducted in humans in the United States under FDA-authorized investigational new drug (IND) applications.

There are ongoing clinical studies of the potential utility of marijuana in medical applications. DHHS states that in 2000, the state of California established the Center for Medicinal Cannabis Research (CMCR) which has funded studies on the potential use of cannabinoids for the treatment of multiple sclerosis, neuropathic pain, appetite suppression and cachexia, and severe pain and nausea related to cancer or its treatment by chemotherapy. To date, though, no NDAs utilizing marijuana for these indications have been submitted to the FDA.

To establish accepted medical use, among other criteria, the effectiveness of a drug must be established in well-controlled scientific studies performed in a large number of patients. To date, such studies have not been performed for marijuana. Small clinical trial studies with limited patients and short duration such as those cited by the petitioner are not sufficient to establish medical utility. Larger studies of longer duration are needed to fully characterize the drug's efficacy and safety profile. Anecdotal reports, patients' self-reported effects, and isolated case reports are not adequate evidence to support an accepted medical use of marijuana (57 FR 10499, 1992).

In addition to demonstrating efficacy, adequate safety studies must be performed to show that the drug is safe for treating the targeted disease. DHHS states that 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 NDA-quality studies that have scientifically assessed the efficacy and full safety profile of marijuana for any medical condition.

DEA further notes that a number of clinical studies from CMCR have been discontinued. Most of these discontinuations were due to

recruitment difficulties (*http://www.cmcr.ucsd.edu/geninfo/research.htm* (last retrieved 07/07/2010) (listing 6 discontinued studies, 5 of which were discontinued because of recruitment issues)).

The petitioner states that the pharmacological effects are well established for marijuana and $\Delta^9$-THC, using the argument that Marinol (containing synthetic $\Delta^9$-THC, known generically as dronabinol) and Cesamet (containing nabilone, a synthetic cannabinoid not found in marijuana) are approved for several therapeutic indications. The approvals of Marinol and Cesamet were based on well-controlled clinical studies that established the efficacy and safety of these drugs as a medicine. Smoked marijuana has not been demonstrated to be safe and effective in treating these medical conditions. Marijuana is a drug substance composed of numerous cannabinoids and other constituents; hence the safety and efficacy of marijuana cannot be evaluated solely on the effects of $\Delta^9$-THC. Adequate and well-controlled studies must be performed with smoked marijuana to establish efficacy and safety. DHHS states that there is a lack of accepted safety for the use of marijuana under medical supervision.

The petitioner has not submitted any new data meeting the requisite scientific standards to support the claim that marijuana has an accepted medical use in the United States. Hence, the new information provided by the petitioner does not change the federal government's evaluation of marijuana's medical use in the United States.

- Petitioner's claim of acceptance of the medical use of marijuana by eight states since 1996 and state officials in these states establishing that marijuana has an accepted medical use in the United States

Petitioner argues that, "[t]he acceptance of cannabis's medical use by eight states since 1996 and the experiences of patients, doctors, and state officials in these states establish marijuana's accepted medical use in the United States." Petition at 10, 13. This argument is contrary to the CSA's statutory scheme. The CSA does not assign to the states the authority to make findings relevant to CSA scheduling determinations. Rather, the CSA expressly delegates the task of making such findings—including whether a substance has any currently accepted medical use in treatment in the United States—to the Attorney General. 21 U.S.C. 811(a). The CSA also expressly tasks the Secretary of DHHS to provide a scientific and medical evaluation and scheduling recommendations to inform the Attorney General's findings. 21 U.S.C. 811(b); *see also* 21 C.F.R. 308.43. That Congress explicitly provided scheduling authority to these two federal entities in this comprehensive and exclusive statutory scheme precludes the argument that state legislative action can establish accepted medical use under the CSA.

The CSA explicitly provides that in making a scheduling determination, the Attorney General shall consider the following eight factors:

1. The drug's actual or relative potential for abuse
2. Scientific evidence of its pharmacological effect, if known;
3. The state of current scientific knowledge regarding the drug;
4. Its history and current pattern of abuse;
5. The scope, duration, and significance of abuse;
6. What, if any, risk there is to the public health;
7. The drug's psychic or physiological dependence liability; and
8. Whether the substance is an immediate precursor of a substance already controlled under the CSA.

21 U.S.C. 811(c). These factors embody Congress's view of the specialized agency expertise required for drug rescheduling decisions. The CSA's statutory text thus further evidences that Congress did not envision such a role for state law in establishing the schedules of controlled substances under the CSA. *See Krumm v. Holder*, 2009 WL 1563381, at *16 (D.N.M. 2009) ("The CSA does not contemplate that state legislatures' determinations about the use of a controlled substance can be used to bypass the CSA's rescheduling process.").

The long-established factors applied by DEA for determining whether a drug has a "currently accepted medical use" under the CSA are:

1. The drug's chemistry must be known and reproducible;
2. There must be adequate safety studies;
3. There must be adequate and well-controlled studies proving efficacy;
4. The drug must be accepted by qualified experts; and
5. The scientific evidence must be widely available.

57 FR 10,499, 10,506 (1992), *ACT*, 15 F.3d at 1135 (upholding these factors as valid criteria for determining "currently accepted medical use"). A drug will be deemed to have a currently accepted medical use for CSA purposes only if all five of the foregoing elements are demonstrated. The following is a summary of information as it relates to each of these five elements.

*1. The drug's chemistry must be known and reproducible*

DHHS states that although the structures 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.

DEA notes that in addition to changes due to its own genetic plasticity, marijuana and its chemistry have been throughout the ages, and continue to be, modified by environmental factors and human manipulation (Paris and Nahas, 1984).

*2. There must be adequate safety studies*

DHHS states that safety studies for acute or subchronic administration of marijuana have been carried out only through a limited number of Phase 1 clinical investigations approved by the FDA. There have been no NDA-quality studies that have scientifically assessed the safety profile of marijuana for any medical condition. DHHS also states that at this time, the known risks of marijuana use have not been shown to be outweighed by specific benefits in well-controlled clinical trials that scientifically evaluate safety and efficacy.

DHHS further states that it 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.

As discussed in Factors 1 and 2, current data suggest that marijuana use produces adverse effects on the respiratory system, memory and learning. Marijuana use is associated with dependence and addiction. In addition, large epidemiological studies indicate that marijuana use may exacerbate symptoms in individuals with schizophrenia.

Therefore DHHS concludes that, even under medical supervision, marijuana has not been shown to have an accepted level of safety. Furthermore, 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.

*3. There must be adequate and well-controlled studies proving efficacy*

DHHS states that no studies have been conducted with marijuana showing efficacy for any indication in controlled, large scale, clinical trials.

To establish accepted medical use, the effectiveness of a drug must be established in well-controlled, well-designed, well-conducted, and well-documented scientific studies, including studies performed in a large number of patients (57 FR 10499, 1992). To date, such studies have not been performed. The small clinical trial studies with limited patients and short duration are not sufficient to establish medical utility. Studies of longer duration are needed to fully characterize the drug's efficacy and safety profile. Scientific reliability must be established in multiple clinical studies. Furthermore, anecdotal reports and isolated case reports are not adequate evidence to support an accepted medical use of marijuana (57 FR 10499, 1992). The evidence from clinical research and reviews of earlier clinical research does not meet this standard.

As noted, DHHS states that a limited number of Phase I investigations have been conducted as approved by the FDA. Clinical trials, however, generally proceed in three phases. *See* 21 C.F.R. 312.21 (2010). Phase I trials encompass initial testing in human subjects, generally involving 20 to 80 patients. *Id.* They are designed primarily to assess initial safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary studies of potential therapeutic benefit. (62 FR 66113, 1997). Phase II and Phase III studies involve successively larger groups of patients: usually no more than several hundred subjects in Phase II and usually from several hundred to several thousand in Phase III. 21 C.F.R. 312.21. These studies are designed primarily to explore (Phase II) and to demonstrate or confirm (Phase III) therapeutic efficacy and benefit in patients. (62 FR 66113, 1997). No Phase II or Phase III studies of marijuana have been conducted. Even in 2001, DHHS acknowledged that 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." (66 FR 20038, 2001). But there is still no data from adequate and well-controlled clinical trials that meets the requisite standard to warrant rescheduling.

DHHS states in a published guidance that it is committed to providing "research-grade marijuana for studies that are the most likely to yield usable, essential data" (DHHS, 1999). DHHS states that the opportunity for scientists to conduct clinical research with botanical marijuana has increased due to changes in the process for obtaining botanical marijuana from NIDA, the only legitimate source of the drug for research in the United States. It further states that 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).

*4. The drug must be accepted by qualified experts*

A material conflict of opinion among experts precludes a finding that marijuana has been accepted by qualified experts (57 FR 10499, 1992). DHHS states that, at this time, it is clear that there is not a consensus of medical opinion concerning medical applications of marijuana, even under conditions where its use is severely restricted. DHHS also concludes that, to date, 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" or a "currently accepted medical use with severe restrictions."

*5. The scientific evidence must be widely available*

DHHS states that the scientific evidence regarding the safety or efficacy of marijuana is typically available only in summarized form, such as in a paper published in the medical literature, rather than in a raw data format. As such, there is no opportunity for adequate scientific scrutiny of whether the data demonstrate safety or efficacy. Furthermore, as stated before, there have only been a limited number of small clinical trials and no controlled, large-scale clinical trials have been conducted with marijuana on its efficacy for any indications or its safety.

In summary, from DHHS's statements on the five cited elements required to make a determination of "currently accepted medical use" for marijuana, DEA has determined that none has been fulfilled. A complete scientific analysis of all the chemical components found in marijuana is still missing. There has been no NDA-quality study that has assessed the efficacy and full safety profile of marijuana for any medical use. At this time, it is clear that there is not a consensus of medical opinion concerning medical applications of marijuana. To date, 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" or even a "currently accepted medical use with severe restrictions." 21 U.S.C. 812(b)(2)(B)). Additionally, scientific evidence as to the safety or efficacy of marijuana is not widely available.

• *Petitioner's claim of increased recognition by health care professionals and the medical community, including the Institute of Medicine (IOM)*

The petitioner states (pg. 15 line 2), "Cannabis's accepted medical use in the United States is increasingly recognized by healthcare professionals and the medical community, including the Institute of Medicine."

DHHS describes that in February 1997, a National Institutes of Health (NIH)-sponsored workshop analyzed available scientific evidence on the potential utility of marijuana. In March 1999, the Institute of Medicine (IOM) issued a detailed report on the potential medical utility of marijuana. Both reports concluded that there need to be more and better studies to determine potential medical applications of marijuana. The IOM report also recommended that clinical trials should be conducted with the goal of developing safe delivery systems (NIH, 1997; IOM, 1999).

DEA notes that in its recommendations, the 1999 IOM report states,

If there is any future for marijuana as a medicine, it lies in its isolated components, the cannabinoids and their synthetic derivatives. Isolated cannabinoids will provide more reliable effects than crude plant mixtures. Therefore, the purpose of clinical trials of smoked marijuana would not be to develop marijuana as a licensed drug but rather to serve as a first step toward the development of nonsmoked rapid-onset cannabinoid delivery systems.

Thus, while the IOM report did support further research into therapeutic uses of cannabinoids, the IOM report did not *"recognize marijuana's accepted medical use"* but rather the potential therapeutic utility of cannabinoids.

DEA notes that the lists presented by the petitioner (pg. 16–18) of "Organizations Supporting *Access* to Therapeutic Cannabis" (emphasis added) and "[Organizations Supporting] No Criminal Penalty" contain a majority of organizations that do not specifically represent medical professionals. By contrast, the petitioner also provides a list of "Organizations Supporting Research on the Therapeutic Use of Cannabis" (emphasis added), which does contain a majority of organizations specifically representing medical professionals.

The petitioner discusses (pg. 20, line 11) the results of a United States survey presented at the annual meeting of the American Society of Addiction Medicine, and states that the study's results,

indicate that physicians are divided on the medical use of cannabis (Reuters of 23 April 2001). Researchers at Rhode Island Hospital in Providence asked 960 doctors about their attitude towards the statement, "Doctors should be able to legally prescribe marijuana as medical therapy." 36 percent of the responders agreed, 38 percent disagreed and 26 percent were neutral.

DEA notes that the results of the study, later published in full (Charuvastra et al., 2005) show that a slight majority of medical doctors polled were opposed to the legalization of medical prescription of marijuana. This supports the finding that there is a material conflict of opinion among medical professionals.

• *Patients' experience in which they reported benefits from smoking marijuana (Exh. C, Section I(3), pg. 22);*

Under the petition's section C. I. 3., the petitioner proposes both anecdotal self-reported effects by patients and clinical studies. The petitioner states (pg. 22, line 2),

[. . .] an increasing number of patients have collected experience with cannabis. Many reported benefits from its use. Some of this experience has been confirmed in reports and clinical investigations or stimulated clinical research that confirmed these patients' experience on other patients suffering from the same disease.

Anecdotal self-reported effects by patients are not adequate evidence for the determination of a drug's accepted medical use. DEA previously ruled in its final order denying the petition of the National Organization for Reform of Marijuana Laws (NORML) to reschedule marijuana from Schedule I to Schedule II of the Controlled Substances Act (57 FR 10499, 1992) that,

Lay testimonials, impressions of physicians, isolated case studies, random clinical experience, reports so lacking in details they cannot be scientifically evaluated, and all other forms of anecdotal proof are entirely irrelevant.

DEA further explained in the same ruling that,

Scientists call [stories by marijuana users who claim to have been helped by the drug] anecdotes. They do not accept them as reliable proofs. The FDA's regulations, for example, provide that in deciding whether a new drug is a safe and effective medicine, "isolated case reports will not be considered." 21 CFR 314.126(e). Why do scientists consider stories from patients and their doctors to be unreliable?

First, sick people are not objective scientific observers, especially when it comes to their own health. [. . .] Second, most of the stories come from people who took marijuana at the same time they took prescription drugs for their symptoms. [. . .] Third, any mind-altering drug that produces euphoria can make a sick person think he feels better. [. . .] Fourth, long-time abusers of marijuana are not immune to illness. [. . .] Thanks to scientific advances and to the passage of the Federal Food, Drug and Cosmetic Act (FDCA) in 1906, 21 U.S.C. 301 et seq., we now rely on rigorous scientific proof to assure the safety and effectiveness of new drugs. Mere stories are not considered an acceptable way to judge whether dangerous drugs should be used as medicines.

Thus, patients' anecdotal experiences with marijuana are not adequate evidence when evaluating whether marijuana has a currently accepted medical use.

In summary, marijuana contains some 483 natural constituents and exists in several forms, including dried leaves and flowering

tops, hashish and hashish oil. It is generally smoked as a cigarette. Research with marijuana is being conducted in humans in the United States under FDA-authorized IND applications, and using marijuana cigarettes provided by NIDA. Adequate studies have not been published to support the safety and efficacy of marijuana as a medicine. No NDA for marijuana has been submitted to the FDA for any indication and thus no medicinal product containing botanical cannabis has been approved for marketing. DEA notes that state laws do not establish a currently accepted medical use under federal law. Furthermore, DEA previously ruled that anecdotal self-reported effects by patients are not adequate evidence of a currently accepted medical use under federal law. A material conflict of opinion among experts precludes a finding that marijuana has been accepted by qualified experts. At present, there is no consensus of medical opinion concerning medical applications of marijuana. In short, the limited number of clinical trials involving marijuana that have been conducted to date—none of which have progressed beyond phase 1 of the three phases needed to demonstrate safety and efficacy for purposes of FDA approval—fails by a large measure to provide a basis for any alteration of the prior conclusions made by HHS and DEA (in 1992 and in 2001) that marijuana has no currently accepted medical use in treatment in the United States.

**FACTOR 4: ITS HISTORY AND CURRENT PATTERN OF ABUSE**

Marijuana use has been relatively stable from 2002 to 2009, and it continues to be the most widely used illicit drug. According to the NSDUH, there were 2.4 million new users (6,000 initiates per day) in 2009 and 16.7 million current (past month) users of marijuana aged 12 and older. Past month use of marijuana was statistically significantly higher in 2009 (16.7 million) than in 2008 (15.2 million), according to NSDUH. An estimated 104.4 million Americans age 12 or older had used marijuana or hashish in their lifetime and 28.5 million had used it in the past year. In 2008, most (62.2 percent) of the 2.2 million new users were less than 18 years of age. In 2008, marijuana was used by 75.7 percent of current illicit drug users and was the only drug used by 57.3 percent of these users. In 2008, among past year marijuana users aged 12 or older, 15.0 percent used marijuana on 300 or more days within the previous 12 months. This translates into 3.9 million people using marijuana on a daily or almost daily basis over a 12-month period. In 2008, among past month marijuana users, 35.7 percent (5.4 million) used the drug on 20 or more days in the past month.

Marijuana is also the illicit drug with the highest rate of past year dependence or abuse. According to the 2009 NSDUH report, 4.3 million persons were classified with marijuana dependence or abuse based on criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM–IV).

According to the 2010 Monitoring the Future (MTF) survey, marijuana is used by a large percentage of American youths. Among students surveyed in 2010, 17.3 percent of eighth graders, 33.4 percent of tenth graders, and 43.8 percent of twelfth graders reported lifetime use (i.e., any use in their lifetime) of marijuana. In addition, 13.7, 27.5 and 34.8 percent of eighth, tenth and twelfth graders, respectively, reported using marijuana in the past year. A number of high-schoolers reported daily use in the past month, including 1.2, 3.3 and 6.1 percent of eighth, tenth and twelfth graders, respectively.

The prevalence of marijuana use and abuse is also indicated by criminal investigations for which drug evidences were analyzed in DEA and state laboratories. The National Forensic Laboratory System (NFLIS), which compiles information on exhibits analyzed in state and local law enforcement laboratories, showed that marijuana was the most frequently identified drug from January 2001 through December 2010: In 2010, marijuana accounted for 36.3 percent (464,059) of all drug exhibits in NFLIS. Similar findings were reported by the System to Retrieve Information from Drug Evidence (STRIDE), a DEA database which compiles information on exhibits analyzed in DEA laboratories, for the same reporting period. From January 2001 through December 2010, marijuana was the most frequently identified drug. In 2010, there were 11,293 marijuana exhibits associated with 7,158 law enforcement cases representing 16.7 percent of all exhibits in STRIDE.

The high consumption of marijuana is being fueled by increasing amounts of domestically grown marijuana as well as increased amounts of foreign source marijuana being illicitly smuggled into the United States. In 2009, the Domestic Cannabis Eradication and Suppression Program (DCE/SP) reported that 9,980,038 plants were eradicated in outdoor cannabis cultivation areas in the United States. Major domestic outdoor cannabis cultivation areas were found in California, Kentucky, Tennessee and Hawaii. Significant quantities of marijuana were also eradicated from indoor cultivation operations. There were 414,604 indoor plants eradicated in 2009 compared to 217,105 eradicated in 2000. Most foreign-source marijuana smuggled into the United States enters through or between points of entry at the United States-Mexico border. However, drug seizure data show that the amount of marijuana smuggled into the United States from Canada via the United States-Canada border has risen to a significant level. In 2009, the Federal-wide Drug Seizure System (FDSS) reported seizures of 1,910,600 kg of marijuana.

While most of the marijuana available in the domestic drug markets is lower potency commercial-grade marijuana, usually derived from outdoor cannabis grow sites in Mexico and the United States, an increasing percentage of the available marijuana is high potency marijuana derived from indoor, closely controlled cannabis cultivation in Canada and the United States. The rising prevalence of high potency marijuana is evidenced by a nearly two-fold increase in average potency of tested marijuana samples, from 4.87 percent $\Delta^9$-THC in 2000 to 8.49 percent $\Delta^9$-THC in 2008.

In summary, marijuana is the most commonly used illegal drug in the United States, and it is used by a large percentage of American high-schoolers. Marijuana is the most frequently identified drug in state, local and federal forensic laboratories, with increasing amounts both of domestically grown and of illicitly smuggled marijuana. An observed increase in the potency of seized marijuana also raises concerns.

**FACTOR 5: THE SCOPE, DURATION, AND SIGNIFICANCE OF ABUSE**

Abuse of marijuana is widespread and significant. DHHS presented data from the NSDUH, and DEA has updated this information. As previously noted, according to the NSDUH, in 2009, an estimated 104.4 million Americans age 12 or older had used marijuana or hashish in their lifetime, 28.5 million had used it in the past year, and 16.7 million (6.6 percent) had used it in the past month. In 2008, an estimated 15.0 percent of past year marijuana users aged 12 or older used marijuana on 300 or more days within the past 12 months. This translates into 3.9 million persons using marijuana on a daily or almost daily basis over a 12-month period. In 2008, an estimated 35.7 percent (5.4 million) of past month marijuana users aged 12 or older used the drug on 20 or more days in the past month (SAMHSA, NSDUH and TEDS). Chronic use of marijuana is associated with a number of health risks (see Factors 2 and 6).

Marijuana's widespread availability is being fueled by increasing marijuana production domestically and increased illicit importation from Mexico and Canada. Domestically both indoor and outdoor grow sites have been encountered. In 2009, nearly 10 million marijuana plants were seized from outdoor grow sites and over 410,000 were seized from indoor sites for a total of over 10 million plants in 2009 compared to about 2.8 million plants in 2000 (Domestic Cannabis Eradication/Suppression Program). An increasing percentage of the available marijuana being trafficked in the United States is higher potency marijuana derived from the indoor, closely controlled cultivation of marijuana plants in both the US and Canada (Domestic Cannabis Eradication/Suppression Program) and the average percentage of $\Delta^9$-THC in seized marijuana increased almost two-fold from 2000 to 2008 (The University of Mississippi Potency Monitoring Project). Additional studies are needed to clarify the impact of greater potency, but DEA notes one study showing that higher levels of $\Delta^9$-THC in the body are associated with greater psychoactive effects (Harder and Rietbrock, 1997), which can be correlated with higher abuse potential (Chait and Burke, 1994).

Data from TEDS show that in 2008, 17.2 percent of all admissions were for primary marijuana abuse. In 2007, more than half of the drug-related treatment admissions involving individuals under the age of 15 (60.8 percent) and more than half of the drug-related treatment admissions involving individuals 15 to 19 years of age (55.9 percent), were for primary marijuana abuse. In 2007, among the marijuana/hashish admissions (286,194), 25.1 percent began using marijuana at age 12 or younger.

In summary, the recent statistics from these various surveys and databases show that

marijuana continues to be the most commonly used illicit drug, with significant rates of heavy use and dependence in teenagers and adults.

The petitioner states, "The use and abuse of cannabis has been widespread in the United States since national drug use surveys began in the 1970s. A considerable number of cannabis users suffer from problems that meet the criteria for abuse. However, the large majority of cannabis users do not experience any relevant problems related to their use." (pg. 4, line 31).

Petitioner acknowledges that a considerable number of cannabis users suffer from problems that meet the criteria for abuse. DEA provides data under this Factor, as well as Factors 1, 2, and 7, that support this undisputed issue. Briefly, current data suggest that marijuana use produces adverse effects on the respiratory system, memory and learning. Marijuana use is associated with dependence and addiction. In addition, large epidemiological studies indicate that marijuana use may exacerbate symptoms in individuals with schizophrenia, and may precipitate schizophrenic disorders in those individuals who are vulnerable to developing psychosis.

**FACTOR 6: WHAT, IF ANY, RISK THERE IS TO THE PUBLIC HEALTH**

The risk marijuana poses to the public health may manifest itself in many ways. Marijuana use may affect the physical and/or psychological functioning of an individual user, but may also have broader public impacts, for example, from a marijuana-impaired driver. The impacts of marijuana abuse and dependence are more disruptive for an abuser, but also for the abuser's family, friends, work environment, and society in general. Data regarding marijuana health risks are available from many sources, including forensic laboratory analyses, crime laboratories, medical examiners, poison control centers, substance abuse treatment centers, and the scientific and medical literature. Risks have been associated with both acute and chronic marijuana use, including risks for the cardiovascular and respiratory systems, as well as risks for mental health and cognitive function and risks related to prenatal exposure to marijuana. The risks of marijuana use and abuse have previously been discussed in terms of the scientific evidence of its pharmacological effects on physical systems under Factor 2. Below, some of the risks of marijuana use and abuse are discussed in broader terms of the effects on the individual user and the public from acute and chronic use of the drug.

**Risks Associated with Acute Use of Marijuana**

DHHS states that acute use of marijuana impairs psychomotor performance, including performance of complex tasks, which makes it inadvisable to operate motor vehicles or heavy equipment after using marijuana (Ramaekers *et al.*, 2004). DHHS further describes a study showing that acute administration of smoked marijuana impairs performance on tests of learning, associative processes, and psychomotor behavior (Block *et al.*, 1992). DHHS also describes studies showing that administration to human volunteers of $\Delta^9$-THC in a smoked marijuana cigarette produced impaired perceptual motor speed and accuracy, two skills that are critical to driving ability (Kurzthaler *et al.*, 1999) and produced increases in disequilibrium measures, as well as in 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 petitioner states that (pg., 65, line 10), "Although the ability to perform complex cognitive operations is assumed to be impaired following acute marijuana smoking, complex cognitive performance after acute marijuana use has not been adequately assessed under experimental conditions." As described above, DHHS presents evidence of marijuana's acute effects on complex cognitive tasks.

DHHS states that dysphoria and psychological distress, including prolonged anxiety reactions, are potential responses in a minority of individuals who use marijuana (Haney *et al.*, 1999). DEA notes reviews of studies describing that some users report unpleasant psychological reactions. Acute anxiety reactions to cannabis may include restlessness, depersonalization, derealization, sense of loss of control, fear of dying, panic and paranoid ideas (see reviews by Thomas, 1993 and Weil, 1970).

DEA notes a review of studies showing that the general depressant effect of moderate to high doses of cannabis might contribute to slowed reaction times, inability to maintain concentration and lapses in attention (see review by Chait and Pierri, 1992). The review suggests that fine motor control and manual dexterity are generally adversely affected although simple reaction time may or may not be. DEA also notes studies showing that choice or complex reaction time is more likely to be affected, with reaction time consistently increasing with the difficulty of the task (e.g., Block and Wittenborn, 1985).

DEA also notes additional studies showing marijuana use interferes with the ability to operate motor vehicles. Studies show that marijuana use can cause impairment in driving (Robbe and O'Hanlon, 1999). The National Highway Traffic Safety Administration (NHTSA) conducted a study with the Institute for Human Psychopharmacology at Maastricht University in the Netherlands (Robbe and O'Hanlon, 1999) to evaluate the effects of low and high doses of smoked $\Delta^9$-THC alone and in combination with alcohol on the following tests: 1) the Road Tracking Test, which measures the driver's ability to maintain a constant speed of 62 mph and a steady lateral position between the boundaries of the right traffic lane; and 2) the Car Following Test, which measures a driver's reaction times and ability to maintain distance between vehicles while driving 164 ft behind a vehicle that executes a series of alternating accelerations and decelerations. Mild to moderate impairment of driving was observed in the subjects after treatment with marijuana. The study found that marijuana in combination with alcohol had an additive effect resulting in severe driving impairment.

DEA also notes a study by Bedard and colleagues (2007), which used a cross-sectional, case-control design with drivers aged 20–49 who were involved in a fatal crash in the United States from 1993 to 2003. Drivers were included if they had been tested for the presence of cannabis and had a confirmed blood alcohol concentration of zero. Cases were drivers who had at least one potentially unsafe driving action recorded in relation to the crash (e.g., speeding); controls were drivers who had no such driving action recorded. Authors calculated the crude and adjusted odds ratios (ORs) of any potentially unsafe driving action in drivers who tested positive for cannabis but negative for alcohol consumption. Five percent of drivers tested positive for cannabis. The crude OR of a potentially unsafe action was 1.39 (99 percent CI = 1.21–1.59) for drivers who tested positive for cannabis. Even after controlling for age, sex, and prior driving record, the presence of cannabis remained associated with a higher risk of a potentially unsafe driving action (1.29, 99 percent CI = 1.11–1.50). Authors of the study concluded that cannabis had a negative effect on driving, as predicted from various human performance studies.

In 2001, estimates derived from the United States Census Bureau and Monitoring the Future show that approximately 600,000 of the nearly 4 million United States high-school seniors drive under the influence of marijuana. Approximately 38,000 seniors reported that they had crashed while driving under the influence of marijuana in 2001 (MTF, 2001).

DEA further notes studies suggesting that marijuana can affect the performance of pilots. Yeswavage and colleagues (1985) evaluated the acute and delayed effects of smoking one marijuana cigarette containing 1.9 percent $\Delta^9$-THC (19 mg of $\Delta^9$-THC) on the performance of aircraft pilots. Ten subjects were trained in a flight simulator prior to marijuana exposure. Flight simulator performance was measured by the number of aileron (lateral control) and elevator (vertical control) and throttle changes, the size of these control changes, the distance off the center of the runaway on landing, and the average lateral and vertical deviation from an ideal glideslope and center line over the final mile of the approach. Compared to the baseline performance, significant differences occurred at 4 hours. Most importantly, at 24 hours after a single marijuana cigarette, there were significant impairments in the number and size of aileron changes, size of elevator changes, distance off-center on landing, and vertical and lateral deviations on approach to landing. Interestingly, despite these performance deficits, the pilots reported no significant subjective awareness of their impairments at 24 hours.

DEA notes a review of the contaminants and adulterants that can be found in marijuana (McPartland, 2002). In particular, DEA notes that many studies have reported contamination of both illicit and NIDA-grown marijuana with microbial contaminants, bacterial or fungal (McLaren *et al.*, 2008; McPartland, 1994, 2002; Ungerleider *et al.*, 1982; Taylor *et al.*, 1982; Kurup *et al.*, 1983). In a study by Kagen and

colleagues (1983), fungi was found in 13 of the 14 samples, and evidence of exposure to Aspergillus fungi was found in the majority of marijuana smokers (13 of 23), but only one of the 10 control participants. Aspergillus can cause aspergillosis, a fatal lung disease and DEA notes studies suggesting an association between this disease and cannabis smoking among patients with compromised immune systems (reviewed in McLaren *et al.*, 2008). Other microbial contaminants include bacteria such as *Klebsiella pneumoniae, salmonella enteritidis,* and group *D Streptococcus* (Ungerlerder *et al.*, 1982; Kagen *et al.*, 1983; Taylor *et al.*, 1982). DEA notes reports that *Salmonella* outbreaks have been linked to marijuana (Taylor *et al.*, 1982, CDC, 1981).

**Risks Associated with Chronic Use of Marijuana**

DHHS states that chronic exposure to marijuana smoke is considered to be comparable to tobacco smoke with respect to increased risk of cancer and lung damage. DEA notes studies showing that marijuana smoke contains several of the same carcinogens and co-carcinogens as tobacco smoke and suggesting that pre-cancerous lesions in bronchial epithelium also seem to be caused by long-term marijuana smoking (Roth *et al.*, 1998). DEA also notes the publication of a recent case-control study of lung cancer in adults (Aldington *et al.*, 2008), in which users reporting over 10.5 joint-years of exposure had a significantly increased risk of developing lung cancer, leading the study's authors to conclude that long-term cannabis use increases the risk of lung cancer in young adults. In addition, a distinctive marijuana withdrawal syndrome has been identified, indicating that marijuana produces physical dependence (Budney *et al.*, 2004), as described in Factor 7.

DHHS further quotes the Diagnostic and Statistical Manual (DSM–IV–TR, 2000) of the American Psychiatric Association, which 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).

In addition, DHHS states that marijuana use produces acute and chronic adverse effects on the respiratory system, memory and learning. Regular marijuana smoking produces a number of long-term pulmonary consequences, including chronic cough and sputum (Adams and Martin, 1996), and histopathologic abnormalities in bronchial epithelium (Adams and Martin, 1996). DEA also notes studies suggesting marijuana use leads to evidence of widespread airway inflammation and injury (Roth *et al.*, 1998, Fligiel *et al.*, 1997) and immunohistochemical evidence of dysregulated growth of respiratory epithelial cells that may be precursors to lung cancer (Baldwin *et al.*, 1997). In addition, very large epidemiological studies indicate that marijuana may increase risk of psychosis in vulnerable populations, i.e., individuals predisposed to develop psychosis (Andreasson *et al.*, 1987) and exacerbate psychotic symptoms in individuals with schizophrenia (Schiffman *et al.*, 2005; Hall *et al.*, 2004; Mathers and Ghodse, 1992; Thornicroft, 1990; see Factor 2).

The petitioner cited "The Missoula Chronic Clinical Cannabis Use Study" as evidence that long-term use of marijuana does not cause significant harm in patients (Russo *et al.*, 2002). DEA notes that this article describes the case histories and clinical examination of only four patients that were receiving marijuana cigarettes from the National Institute on Drug Abuse for a variety of medical conditions. The number of patients included in the study is not adequate for this evaluation.

The petitioner states, "Studies have shown the long-term use of cannabis to be safe. In contrast to many other medicinal drugs, the long-term use of cannabis does not harm stomach, liver, kidneys and heart." (Exh. C, Section II (10), pg. 66).

However, DHHS states that marijuana has not been shown to have an accepted level of safety for medical use. There have been no NDA-quality studies that have scientifically assessed the full safety profile of marijuana for any medical condition. DEA notes in addition, as described above, the risks associated with chronic marijuana use, including, as described in Factor 2, risks for the cardiovascular and respiratory systems, as well as risks for mental health and cognitive function and risks related to prenatal exposure to marijuana.

**Marijuana as a "Gateway Drug"**

A number of studies have examined the widely held premise that marijuana use leads to subsequent abuse of other illicit drugs, thus functioning as a "gateway drug." DHHS discussed a 25-year study of 1,256 New Zealand children, Fergusson *et al.* (2005), which concluded that the use of marijuana correlates to an increased risk of abuse of other drugs. Other studies, however, do not support a direct causal relationship between regular marijuana use and other illicit drug abuse. DHHS cited the IOM report (1999), which states that marijuana is a "gateway drug" in the sense that its use typically precedes rather than follows initiation of other illicit drug use. However, as cited by DHHS, the IOM states that, "[t]here is no conclusive evidence that the drug effects of marijuana are causally linked to the subsequent abuse of other illicit drugs." DHHS noted that for most studies that test the hypothesis that marijuana causes abuse of harder drugs, the determinative measure for testing this hypothesis is whether marijuana leads to "any drug use" rather than that marijuana leads to "drug abuse and dependence" as defined by DSM–IV criteria.

**FACTOR 7: ITS PSYCHIC OR PHYSIOLOGICAL DEPENDENCE LIABILITY**

DHHS states that many medications that are not associated with abuse or addiction, such as antidepressants, beta-blockers, and centrally acting antihypertensive drugs, can produce physical dependence and withdrawal symptoms after chronic use. However, psychological and physical dependence of drugs that have abuse potential are important factors contributing to increased or continued drug taking. This section provides scientific evidence that marijuana causes physical and psychological dependence.

**Physiological (Physical) Dependence in Humans**

Physical dependence is a state of adaptation manifested by a drug class-specific withdrawal syndrome produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist (American Academy of Pain Medicine, American Pain Society and American Society of Addiction Medicine consensus document, 2001).

DHHS states that long-term, regular use of marijuana can lead to physical dependence and withdrawal following discontinuation as well as psychic addiction or dependence. The marijuana withdrawal syndrome consists of symptoms such as restlessness, irritability, mild agitation, insomnia, EEG disturbances, nausea, cramping and decrease in mood and appetite that may resolve after 4 days, and may require in-hospital treatment (Haney *et al.*, 1999). It is distinct and mild compared to the withdrawal syndromes associated with alcohol and heroin use (Budney *et al.*, 1999; Haney *et al.*, 1999). DEA notes that Budney *et al.* (1999) examined the withdrawal symptomatology in 54 chronic marijuana abusers seeking treatment for their dependence. The majority of the subjects (85 percent) reported that they had experienced symptoms of at least moderate severity. Fifty seven percent (57 percent) reported having six or more symptoms of a least moderate severity while 47 percent experienced four or more symptoms rated as severe. The most reported mood symptoms associated with the

withdrawal were irritability, nervousness, depression, and anger. Some of the other behavioral characteristics of the marijuana withdrawal syndrome were craving, restlessness, sleep disruptions, strange dreams, changes in appetite, and violent outbursts.

DHHS discusses a study by Lane and Phillips-Bute (1998) which describes milder cases of dependence including symptoms that are comparable to those from caffeine withdrawal, including decreased vigor, increased fatigue, sleepiness, headache, and reduced ability to work. The marijuana withdrawal syndrome has been reported in adolescents who were admitted for substance abuse treatment or in individuals who had been given marijuana on a daily basis during research conditions. Withdrawal symptoms can also be induced in animals following administration of a cannabinoid antagonist after chronic $\Delta^9$-THC administration (Maldonado, 2002; Breivogel *et al.*, 2003). DHHS also discusses a study comparing marijuana and tobacco withdrawal symptoms in humans (Vandrey *et al.*, 2005) which demonstrated that the magnitude and time course of the two withdrawal syndromes are similar.

DHHS states that a review by Budney and colleagues (2004) of studies of cannabinoid withdrawal, with a particular emphasis on human studies, led to the recommendation that the Diagnostic and Statistical Manual of Mental Disorders (DSM) introduce a listing for cannabis withdrawal. In this listing, common symptoms would include anger or aggression, decreased appetite or weight loss, irritability, nervousness/anxiety, restlessness and sleep difficulties including strange dreams. Less common symptoms/equivocal symptoms would include chills, depressed mood, stomach pain, shakiness and sweating.

**Psychological Dependence in Humans**

In addition to physical dependence, DHHS states that long-term, regular use of marijuana can lead to psychic addiction or dependence. Psychological dependence on marijuana is defined by the American Psychiatric Association in the DSM–IV and cited by DHHS.

The Diagnostic and Statistical Manual of Mental Disorders (DSM–IV) is published by the American Psychiatric Association (2000), and provides diagnostic criteria to improve the reliability of diagnostic judgment of mental disorders by mental health professionals. DSM–IV currently defines "Cannabis Dependence" (DSM–IV diagnostic category 304.30) as follows:

Cannabis dependence: A destructive pattern of cannabis use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring when the cannabis use was at its worst:

1. Cannabis tolerance, as defined by either of the following:

a. A need for markedly increased amounts of cannabis to achieve intoxication,

b. Markedly diminished effect with continued use of the same amount of cannabis.

2. Greater use of cannabis than intended: Cannabis was often taken in larger amounts or over a longer period than was intended.

3. Unsuccessful efforts to cut down or control cannabis use: Persistent desire or unsuccessful efforts to cut down or control cannabis use.

4. Great deal of time spent in using cannabis, or recovering from hangovers.

5. Cannabis caused reduction in social, occupational or recreational activities: Important social, occupational, or recreational activities given up or reduced because of cannabis use.

6. Continued using cannabis despite knowing it caused significant problems: Cannabis use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been worsened by cannabis.

In addition, the DSM–IV added a specifier to this diagnostic by which it can be with or without physiological (physical) dependence.

DEA notes additional clinical studies showing that frequency of $\Delta^9$-THC use (most often as marijuana) escalates over time. Individuals increase the number, doses, and potency of marijuana cigarettes. Several studies have reported that patterns of marijuana smoking and increased quantity of marijuana smoked were related to social context and drug availability (Kelly *et al.*, 1994; Mendelson and Mello, 1984; Mello, 1989).

DEA further notes that Budney *et al.* (1999) reported that 93 percent of marijuana-dependent adults seeking treatment reported experiencing mild craving for marijuana, and 44 percent rated their past craving as severe. Craving for marijuana has also been documented in marijuana users not seeking treatment (Heishman *et al.*, 2001). Two hundred seventeen marijuana users completed a 47-item Marijuana Craving Questionnaire and forms assessing demographics, drug use history, marijuana-quit attempts and current mood. The results indicate that craving for marijuana was characterized by 1) the inability to control marijuana use (compulsivity); 2) the use of marijuana in anticipation of relief from withdrawal or negative mood (emotionality); 3) anticipation of positive outcomes from smoking marijuana (expectancy); and 4) intention and planning to use marijuana for positive outcomes (purposefulness).

In summary, long-term, regular use of marijuana can lead to physical dependence and withdrawal following discontinuation as well as psychic addiction or dependence.

**FACTOR 8: WHETHER THE SUBSTANCE IS AN IMMEDIATE PRECURSOR OF A SUBSTANCE ALREADY CONTROLLED UNDER THE CSA**

Marijuana is not an immediate precursor of any controlled substance.

**DETERMINATION**

After consideration of the eight factors discussed above and of DHHS's recommendation, DEA 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):

**1. Marijuana has a high potential for abuse**

Marijuana is the most highly abused and trafficked illicit substance in the United States. Approximately 16.7 million individuals in the United States (6.6 percent of the United States population) used marijuana monthly in 2009. A 2009 national survey that tracks drug use trends among high school students showed that by 12th grade, 32.8 percent of students reported having used marijuana in the past year, 20.6 percent reported using it in the past month, and 5.2 percent reported having used it daily in the past month. Its widespread availability is being fueled by increasing marijuana production domestically and increased trafficking from Mexico and Canada.

Marijuana has dose-dependent reinforcing effects that encourage its abuse. Both clinical and preclinical studies have clearly demonstrated that marijuana and its principle psychoactive constituent, $\Delta^9$-THC, possess the pharmacological attributes associated with drugs of abuse. They function as discriminative stimuli and as positive reinforcers to maintain drug use and drug-seeking behavior.

Significant numbers of chronic users of marijuana seek substance abuse treatment. Compared to all other specific drugs included in the 2008 NSDUH survey, marijuana had the highest levels of past year dependence and abuse.

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

DHHS states that the FDA has not evaluated nor approved an NDA for marijuana. The long-established factors applied by DEA for determining whether a drug has a "currently accepted medical use" under the CSA are as follows. A drug will be deemed to have a currently accepted medical use for CSA purposes only if all of the following five elements have been satisfied. As set forth below, none of these elements has been fulfilled:

*i. The drug's chemistry must be known and reproducible*

Although the structures 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. Furthermore, many variants of the marijuana plant are found due to its own genetic plasticity and human manipulation.

*ii. There must be adequate safety studies*

Safety studies for acute or sub-chronic administration of marijuana have been carried out through a limited number of Phase I clinical investigations approved by the FDA, but there have been no NDA-quality studies that have scientifically assessed the full safety profile of marijuana for any medical condition. Large, controlled studies have not been conducted to evaluate the risk-benefit ratio of marijuana use, and any potential benefits attributed to marijuana use currently do not outweigh the known risks.

*iii. There must be adequate and well-controlled studies proving efficacy*

DHHS states that there have been no NDA-quality studies that have scientifically assessed the efficacy of marijuana for any medical condition. To establish accepted medical use, the effectiveness of a drug must be established in well-controlled, well-

designed, well-conducted, and well-documented scientific studies, including studies performed in a large number of patients. To date, such studies have not been performed for any indications.

Small clinical trial studies with limited patients and short duration are not sufficient to establish medical utility. Studies of longer duration are needed to fully characterize the drug's efficacy and safety profile. Scientific reliability must be established in multiple clinical studies. Anecdotal reports and isolated case reports are not sufficient evidence to support an accepted medical use of marijuana. The evidence from clinical research and reviews of earlier clinical research does not meet the requisite standards.

*iv. The drug must be accepted by qualified experts*

At this time, it is clear that there is no consensus of opinion among experts concerning medical applications of marijuana. To date, 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" or a "currently accepted medical use with severe restrictions.

*v. The scientific evidence must be widely available*

DHHS states that the scientific evidence regarding the safety and efficacy of marijuana is typically available only in summarized form, such as in a paper published in the medical literature, rather than in a raw data format. In addition, as noted, there have only been a limited number of small clinical trials and no controlled, large scale, clinical trials have been conducted with marijuana on its efficacy for any indications or its safety.

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

At present, there are no FDA-approved marijuana products, nor is marijuana under NDA evaluation at the FDA for any indication. Marijuana does not have a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions. The Center for Medicinal Cannabis Research in California, among others, is conducting research with marijuana at the IND level, but these studies have not yet progressed to the stage of submitting an NDA. Current data suggest that marijuana use produces adverse effects on the respiratory system, memory and learning. Marijuana use is associated with dependence and addiction. In addition, very large epidemiological studies indicate that marijuana use may be a causal factor for the development of psychosis in individuals predisposed to develop psychosis and may exacerbate psychotic symptoms in individuals with schizophrenia. Thus, at this time, the known risks of marijuana use have not been shown to be outweighed by specific benefits in well-controlled clinical trials that scientifically evaluate safety and efficacy. In sum, at present, marijuana lacks an acceptable level of safety even under medical supervision.

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