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DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Office of the Assistant Secretary for Health
Washington, D.C. 20201

JUN 25 2015

EXHIBIT
252

The Honorable Chuck Rosenberg
Acting Administrator
Drug Enforcement Administration
U.S. Department of Justice
8701 Morrissette Drive
Springfield, VA 22152

Dear Mr. Rosenberg:

Pursuant to the Controlled Substances Act (CSA, 21 U.S.C. § 811(b), (c), and (f)), the Department of Health and Human Services (HHS) is recommending that marijuana continue to be maintained in Schedule I of the CSA.

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FRANKIE H. GRAY, CLERK

The Food and Drug Administration (FDA) has considered the abuse potential and dependence-producing characteristics of marijuana.

Marijuana meets 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 enclosed analyses, marijuana has a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision. Accordingly, HHS recommends that marijuana be maintained in Schedule I of the CSA. Enclosed are two documents prepared by FDA's Controlled Substance Staff (in response to petitions filed in 2009 by Mr. Bryan Krumm and in 2011 by Governors Lincoln D. Chafee and Christine O. Gregoire) that form the basis for the recommendation. Pursuant to the requests in the petitions, FDA broadly evaluated marijuana, and did not focus its evaluation on particular strains of marijuana or components or derivatives of marijuana.

FDA's Center for Drug Evaluation and Research's current review of the available evidence and the published clinical studies on marijuana demonstrated that since our 2006 scientific and medical evaluation and scheduling recommendation responding to a previous DEA petition, research with marijuana has progressed. However, the available evidence is not sufficient to determine that marijuana has an accepted medical use. Therefore, more research is needed into marijuana's effects, including potential medical uses for marijuana and its derivatives. Based on the current review, we identified several methodological challenges in the marijuana studies published in the literature. We recommend they be addressed in future clinical studies with marijuana to ensure that valid scientific data are generated in studies evaluating marijuana's safety and efficacy for therapeutic use. For example, we recommend that studies need to focus on consistent administration and reproducible dosing of marijuana, potentially through the use of

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administration methods other than smoking. A summary of our review of the published literature on the clinical uses of marijuana, including recommendations for future studies, is attached to this document.

FDA and the National Institutes of Health's National Institute on Drug Abuse (NIDA) also believe that work continues to be needed to ensure support by the federal government for the efficient conduct of clinical research using marijuana. Concerns have been raised about whether the existing federal regulatory system is flexible enough to respond to increased interest in research into the potential therapeutic uses of marijuana and marijuana-derived drugs. HHS welcomes an opportunity to continue to explore these concerns with DEA.

Should you have any questions regarding these recommendations, please contact Corinne P. Moody, Science Policy Analyst, Controlled Substance Staff, Center for Drug Evaluation and Research, FDA, at (301) 796-3152.

Sincerely yours,

Karen B. DeSalvo, MD, MPH, MSc
Acting Assistant Secretary for Health

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Enclosures

ENCLOSURE 1

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

On November 30, 2011, Governors Lincoln D. Chafee of Rhode Island and Christine O. Gregoire of Washington 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 marijuana has an accepted medical use in the United States, is safe for use under medical supervision, and has a relatively low abuse potential compared to other Schedule II drugs. The petition requests that marijuana and "related items" be rescheduled in Schedule II of the CSA. In June 2013, the DEA Administrator requested that the U.S. 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*)[1] under the CSA. Pursuant to 21 U.S.C. 811(b), the Secretary of HHS 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 or transferring a substance from one schedule to another. 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 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.

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[1] The CSA defines marihuana (marijuana) as the following:

> All parts of the plant Cannabis sativa L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin. Such term does not include the mature stalks of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination (21 U.S.C. 802(16)).

1. Its Actual or Relative Potential For Abuse

Under the first factor, the Secretary must consider marijuana's actual or relative potential for abuse. The CSA does not define the term "abuse." However, the CSA's legislative history suggests the following in determining whether a particular drug or substance has a potential for abuse[2]:

a. There is evidence that individuals are taking the drug or drugs containing such a 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 drugs containing such a substance from legitimate drug channels.

c. Individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice.

d. The drug or drugs containing such a substance are new drugs so related in their action to a drug or drugs already listed as having a potential for abuse to make it likely that the drug will have the same potentiality 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.

In the development of this scientific and medical evaluation for the purpose of scheduling, the Secretary analyzed considerable data related to the substance's abuse potential. The data include a discussion of the prevalence and frequency of use, the amount of the substance available for illicit use, the ease of obtaining or manufacturing the substance, the reputation or status of the substance "on the street," and evidence relevant to at-risk populations. Importantly, the petitioners define marijuana as including all *Cannabis* cultivated strains. Different marijuana samples derived from various cultivated strains may have very different chemical constituents, thus the analysis is based on what is known about the range of these constituents across all cultivated strains.

Determining the abuse potential of a substance is complex with many dimensions, and no single test or assessment provides a complete characterization. Thus, no single measure of abuse potential is ideal. Scientifically, a comprehensive evaluation of the relative abuse potential of a substance can include consideration of the following elements: receptor binding affinity, preclinical pharmacology, reinforcing effects, discriminative stimulus effects, dependence producing potential, pharmacokinetics, route of administration, toxicity, data on

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

actual abuse, clinical abuse potential studies, and public health risks. Importantly, abuse can exist independently from tolerance or physical dependence because individuals may abuse drugs in doses or patterns that do not induce these phenomena. Additionally, evidence of clandestine production and illicit trafficking of a substance can shed light on both the demand for a substance as well as the ease of obtaining a substance. Animal and human laboratory data and epidemiological data are all used in determining a substance's abuse potential. Moreover, epidemiological data can indicate actual abuse.

The petitioners compare the effects of marijuana to currently controlled Schedule II substances and make repeated claims about their comparative effects. Comparisons between marijuana and the diverse array of Schedule II substances is difficult, because of the pharmacologically dissimilar actions of substances in Schedule II of the CSA. For example, Schedule II substances include stimulant-like drugs (e.g., cocaine, methylphenidate, and amphetamine), opioids (e.g., oxycodone, fentanyl), sedatives (e.g., pentobarbital, amobarbital), dissociative anesthetics (e.g., PCP), and naturally occurring plant components (e.g., coca leaves and poppy straw). The mechanism(s) of action of the above Schedule II substances are wholly different from one another, and they are different from tetrahydrocannabinol (THC) and marijuana as well. For example, Schedule II stimulants typically function by increasing monoaminergic tone via an increase in dopamine and norepinephrine (Schmitt et al., 2013). In contrast, opioid analgesics function via mu-opioid receptor agonist effects. These differing mechanism(s) of action result in vastly different behavioral and adverse effect profiles, making comparisons across the range of pharmacologically diverse C-II substances inappropriate.

In addition, many substances scheduled under the CSA are reviewed and evaluated within the context of commercial drug development, using data submitted in the form of a new drug application (NDA). A new analgesic drug might be compared to a currently scheduled analgesic drug as part of the assessment of its relative abuse potential. However, because the petitioners have not identified a specific indication for the use of marijuana, identifying an appropriate comparator based on indication cannot be done.

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.

Evidence shows that some individuals are taking marijuana in amounts sufficient to create a hazard to their health and to the safety of other individuals and the community. A large number of individuals use marijuana. HHS provides data on the extent of marijuana abuse through NIDA and the Substance Abuse and Mental Health Services Administration (SAMHSA). According to the most recent data from SAMHSA's 2012 National Survey on Drug Use and Health (NSDUH), which estimates the number of individuals who have used a substance within the month prior to the study (described as "current use"), marijuana is the most commonly used illicit drug among Americans aged 12 years and older, with an estimated 18.9 million Americans having used marijuana within the month prior to the 2012 NSDUH. Compared to 2004, when an estimated 14.6 million individuals reported using marijuana within the month prior to the study, the estimated rates in 2012 show an increase of approximately 4.3 million individuals. The 2013 Monitoring the Future (MTF) survey of

8th, 10th, and 12th grade students also indicates that marijuana is the most widely used illicit substance in this age group. Specifically, current monthly use was at 7.0 percent of 8th graders, 18.0 percent of 10th, graders and 22.7 percent of 12th graders. Additionally, the 2011 Treatment Episode Data Set (TEDS) reported that primary marijuana abuse accounted for 18.1 percent of non-private substance-abuse treatment facility admissions, with 24.3 percent of those admitted reporting daily use. However, of these admissions for primary marijuana abuse, the criminal justice system referred 51.6 percent to treatment. SAMHSA's Drug Abuse Warning Network (DAWN) was a national probability survey of U.S. hospitals with emergency departments (EDs), and was designed to obtain information on ED visits where recent drug use was implicated. In 2011, there were 455,668 ED visits in which marijuana was mentioned, accounting for 36.4 percent of illicit drug related ED visits. There are some limitations related to DAWN data on ED visits, which are discussed in detail in Factor 4, "Its History and Current Patterns of Abuse." For more information, refer to 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." These factors contain detailed discussions of these data.

A number of risks can occur with both acute and chronic use of marijuana. Detailed discussions of the risks are addressed in Factor 2, "Scientific Evidence of its Pharmacological Effect, if Known," and Factor 6, "What, if any, Risk There is to the Public Health."

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

There is a lack of evidence of significant diversion of marijuana from legitimate drug channels, but this is likely due to the fact that marijuana is more widely available from illicit sources rather than through legitimate channels. Marijuana is not an FDA-approved drug product, as an NDA or biologics license application (BLA) has not been approved for marketing in the United States. Numerous states and the District of Columbia have state-level medical marijuana laws that allow for marijuana use within that state. These state-level drug channels do not have sufficient and complete data to allow for an analysis of diversion, nor is there sufficient collection of data related to medical treatment, including efficacy and safety.

Marijuana is used by researchers for nonclinical research as well as clinical research under investigational new drug (IND) applications; this represents the only legitimate drug channel in the United States. However, marijuana used for research represents a very small contribution of the total amount of marijuana available in the United States, and thus provides limited information about diversion. In addition, the lack of significant diversion of investigational supplies is likely because of the widespread availability of illicit marijuana of equal or greater amounts of delta^9-THC. The data originating from the DEA on seizure statistics demonstrate the magnitude of the availability for illicit marijuana. DEA's System to Retrieve Information from Drug Evidence (STRIDE) provides information on total domestic drug seizures. STRIDE reports a total domestic seizure of 573,195 kg of marijuana in 2011, the most recent year with complete data that is currently publically available (DEA Domestic Drug Seizures, n.d.).

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.

Because the FDA has not approved an NDA or BLA for a marijuana drug product for any therapeutic indication, the only way an individual can take marijuana on the basis of medical advice through legitimate channels at the federal level is by participating in research under an IND application. That said, numerous states and the District of Columbia have passed state-level medical marijuana laws allowing for individuals to use marijuana under certain circumstances. However, data are not yet available to determine the number of individuals using marijuana under these state-level medical marijuana laws. Regardless, according to the 2012 NSDUH data, 18.9 million American adults currently use marijuana (SAMHSA, 2013). Based on the large number of individuals reporting current use of marijuana and the lack of an FDA-approved drug product in the United States, one can assume that it is likely that the majority of individuals using marijuana do so on their own initiative rather than on the basis of medical advice from a licensed practitioner.

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.

FDA has approved two drug products containing cannabinoid compounds that are structurally related to the active components in marijuana. These two marketed products are controlled under the CSA. Once a specific drug product containing cannabinoids becomes approved, that specific drug product may be moved from Schedule I to a different Schedule (II – V) under the CSA. Firstly, Marinol—generically known as dronabinol—is a Schedule III drug product containing synthetic delta^{9}-THC. Marinol, which is formulated in sesame oil in soft gelatin capsules, was first placed in Schedule II under the CSA following its approval by the FDA. Marinol was later rescheduled to Schedule III under the CSA because of low numbers of reports of abuse relative to marijuana. Dronabinol is listed in Schedule I under the CSA. FDA approved Marinol in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who failed to respond adequately to conventional anti-emetic treatments. In 1992, FDA approved Marinol for anorexia associated with weight loss in patients with acquired immunodeficiency syndrome (AIDS). Secondly, in 1985, FDA approved Cesamet, a drug product containing the Schedule II substance nabilone, for the treatment of nausea and vomiting associated with cancer chemotherapy. Besides the two cannabinoid-containing drug products FDA approved for marketing, other naturally occurring cannabinoids and their derivatives (from *Cannabis*) and their synthetic equivalents with similar chemical structure and pharmacological activity are included in the CSA as Schedule I substances.

2. SCIENTIFIC EVIDENCE OF ITS PHARMACOLOGICAL EFFECTS, IF KNOWN

Under the second factor, the Secretary must consider the scientific evidence of marijuana's pharmacological effects. Abundant scientific data are 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 current research literature on cannabinoids available in the public domain.

Neurochemistry and Pharmacology of Marijuana

Marijuana is a plant that contains numerous natural constituents, such as cannabinoids, that have a variety of pharmacological actions. The petition defines marijuana as including all *Cannabis* cultivated strains. Different marijuana samples derived from various cultivated strains may have very different chemical constituents including delta^9-THC and other cannabinoids (Appendino et al., 2011). As a consequence, marijuana products from different strains will have different biological and pharmacological profiles.

According to ElSohly and Slade (2005) and Appendino et al. (2011), marijuana contains approximately 525 identified natural constituents, including approximately 100 compounds classified as cannabinoids. Cannabinoids primarily exist in *Cannabis*, and published data suggests that most major cannabinoid compounds occurring naturally have been identified chemically. New and minor cannabinoids and other new compounds are continuously being characterized (Pollastro et al., 2011). So far, only two cannabinoids (cannabigerol and its corresponding acid) have been obtained from a non-*Cannabis* source. A South African *Helichrysum* (*H. umbraculigerum*) accumulates these compounds (Appendino et al., 2011). The chemistry of marijuana is described in more detail in Factor 3, "The State of Current Scientific Knowledge Regarding the Drug or Other Substance."

The site of cannabinoid action is at the cannabinoid receptors. Cloning of cannabinoid receptors, first from rat brain tissue (Matsuda et al., 1990) and then from human brain tissue (Gerard et al., 1991), has verified the site of action. Two cannabinoid receptors, CB_1 and CB_2, were characterized (Battista et al., 2012; Piomelli, 2005). Evidence of a third cannabinoid receptor exists, but it has not been identified (Battista et al., 2012).

The cannabinoid receptors, CB_1 and CB_2, belong to the family of G-protein-coupled receptors, and present a typical seven transmembrane-spanning domain structure. Cannabinoid receptors link to an inhibitory G-protein (G_i), such that adenylate cyclase activity is inhibited when a ligand binds to the receptor. This, in turn, prevents the conversion of ATP to the second messenger, cyclic AMP (cAMP). Examples of inhibitory-coupled receptors include opioid, muscarinic cholinergic, alpha$_2$-adrenoreceptors, dopamine (D_2), and serotonin (5-HT_1).

Cannabinoid receptor activation inhibits N- and P/Q-type calcium channels and activates inwardly rectifying potassium channels (Mackie et al., 1995; Twitchell et al., 1997). N-type

calcium channel inhibition decreases neurotransmitter release from several tissues. Thus, calcium channel inhibition may be the mechanism by which cannabinoids inhibit acetylcholine, norepinephrine, and glutamate release from specific areas of the brain. These effects may represent a potential cellular mechanism underlying cannabinoids' antinociceptive and psychoactive effects (Ameri, 1999).

CB_1 receptors are found primarily in the central nervous system, but are also present in peripheral tissues. CB_1 receptors are located mainly in the basal ganglia, hippocampus, and cerebellum of the brain (Howlett et al., 2004). The localization of these receptors may explain cannabinoid interference with movement coordination and effects on memory and cognition. Additionally, CB_1 receptors are found in the immune system and numerous other peripheral tissues (Petrocellis and Di Marzo, 2009). However, the concentration of CB_1 receptors is considerably lower in peripheral tissues than in the central nervous system (Herkenham et al., 1990 and 1992).

CB_2 receptors are found primarily in the immune system, but are also present in the central nervous system and other peripheral tissues. In the immune system, CB_2 receptors are found predominantly in B lymphocytes and natural killer cells (Bouaboula et al., 1993). CB_2 receptors may mediate cannabinoids' immunological effects (Galiegue et al., 1995). Additionally, CB_2 receptors have been localized in the brain, primarily in the cerebellum and hippocampus (Gong et al., 2006). The distribution of CB_2 receptors throughout the body is less extensive than the distribution of CB_1 receptors (Petrocellis and Di Marzo, 2009). However, both CB_1 and CB_2 receptors are present in numerous tissues of the body.

Cannabinoid receptors have endogenous ligands. In 1992 and 1995, two endogenous cannabinoid receptor agonists, anandamide and arachidonyl glycerol (2-AG), respectively, were identified (Di Marzo, 2006). Anandamide is a low efficacy agonist (Breivogel and Childers, 2000) and 2-AG is a high efficacy agonist (Gonsiorek et al., 2000). Cannabinoid endogenous ligands are present in central as well as peripheral tissues. A combination of uptake and hydrolysis terminate the action of the endogenous ligands. The endogenous cannabinoid system is a locally active signaling system that, to help restore homeostasis, is activated "on demand" in response to changes to the local homeostasis (Petrocellis and Di Marzo, 2009). The endogenous cannabinoid system, including the endogenous cannabinoids and the cannabinoid receptors, demonstrate substantial plasticity in response to several physiological and pathological stimuli (Petrocellis and Di Marzo, 2009). This plasticity is particularly evident in the central nervous system.

Delta^9-THC and cannabidiol (CBD) are two abundant cannabinoids present in marijuana. Marijuana's major psychoactive cannabinoid is delta^9-THC (Wachtel et al., 2002). In 1964, Gaoni and Mechoulam first described delta^9-THC's structure and function. In 1963, Mechoulam and Shvo first described CBD's structure. The pharmacological actions of CBD have not been fully studied in humans.

Delta^9-THC and CBD have varying affinity and effects at the cannabinoid receptors. Delta^9-THC displays similar affinity for CB_1 and CB_2 receptors, but behaves as a weak agonist for CB_2 receptors. 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 activation of CB_1-receptors mediates cannabinoids' psychotropic effects (Hanus et al., 1999). CBD has low affinity for both CB_1 and CB_2 receptors (Mechoulam et al., 2007). According to Mechoulam et al. (2007), CBD has antagonistic effects at CB_1 receptors and some inverse agonistic properties at CB_2 receptors. When cannabinoids are given subacutely to rats, CB_1 receptors down-regulate and the binding of the second messenger system coupled to CB_1 receptors, GTPgammaS, decreases (Breivogel et al., 2001).

Animal Behavioral Effects

Self-Administration

Self-administration is a method that assesses the ability of a drug to produce rewarding effects. The presence of rewarding effects increases the likelihood of behavioral responses to obtain additional drug. Animal self-administration of a drug is often useful in predicting rewarding effects in humans, and is indicative of abuse liability. A good correlation is often observed between those drugs that rhesus monkeys self-administer and those drugs that humans abuse (Balster and Bigelow, 2003). Initially, researchers could not establish self-administration of cannabinoids, including delta^9-THC, in animal models. However, self-administration of delta^9-THC can now be established in a variety of animal models under specific training paradigms (Justinova et al., 2003, 2004, 2005).

Squirrel monkeys, with and without prior exposure to other drugs of abuse, self-administer delta^9-THC under specific conditions. For instance, Tanda et al. (2000) observed that when squirrel monkeys are initially trained to self-administer intravenous cocaine, they will continue to bar-press delta^9-THC at the same rate as they would with cocaine. The doses were notably comparable to those doses used by humans who smoke marijuana. SR141716, a CB_1 cannabinoid receptor agonist-antagonist, can block this rewarding effect. Other studies show that naïve squirrel monkeys can be successfully trained to self-administer delta^9-THC intravenously (Justinova et al., 2003). The maximal responding rate is 4 μg/kg per injection, which is 2-3 times greater than observed in previous studies using cocaine-experienced monkeys. Naltrexone, a mu-opioid antagonist, partially antagonizes these rewarding effects of delta^9-THC (Justinova et al., 2004).

Additionally, data demonstrate that under specific conditions, rodents self-administer cannabinoids. Rats will self-administer delta^9-THC when applied intracerebroventricularly (i.c.v.), but only at the lowest doses tested (0.01-0.02 μg /infusion) (Braida et al., 2004). SR141716 and the opioid antagonist naloxone can antagonize this effect. However, most studies involve rodents self-administrating the synthetic cannabinoid WIN 55212, a CB_1 receptor agonist with a non-cannabinoid structure (Deiana et al., 2007; Fattore et al., 2007; Martellotta et al., 1998; Mendizabal et al., 2006).

Aversive effects, rather than reinforcing effects, occur in rats that received high doses of WIN 55212 (Chaperon et al., 1998) or delta^9-THC (Sanudo-Pena et al., 1997), indicating a possible critical dose-dependent effect. In both studies, SR141716 reversed these aversive effects.

Conditioned Place Preference

Conditioned place preference (CPP) is a less rigorous method than self-administration for determining whether or not a drug has rewarding properties. In this behavioral test, animals 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, rather than with the placebo, when presented with both options simultaneously.

Animals show CPP to delta^9-THC, but only at the lowest doses tested (0.075-1.0 mg/kg, intraperitoneal (i.p.)) (Braida et al., 2004). SR141716 and naloxone antagonize this effect (Braida et al., 2004). As a partial agonist, SR141716 can induce CPP at doses of 0.25, 0.5, 2 and 3 mg/kg (Cheer et al., 2000). In knockout mice, those without μ-opioid receptors do not develop CPP to delta^9-THC (Ghozland et al., 2002).

Drug Discrimination Studies

Drug discrimination is a method where 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. To determine whether the test drug is like the known drug of abuse, a challenge session with the test drug demonstrates which of the two bars the animal presses more often.

In addition to humans (Lile et al., 2009; Lile et al., 2011), it has been noted that animals, including monkeys (McMahon, 2009), mice (McMahon et al., 2008), and rats (Gold et al., 1992), are able to discriminate cannabinoids from other drugs or placebo. Moreover, the major active metabolite of delta^9-THC, 11-hydroxy-delta^9-THC, also generalizes (following oral administration) to the stimulus cues elicited by delta^9-THC (Browne and Weissman, 1981). Twenty-two other cannabinoids found in marijuana also fully substitute for delta^9-THC. However, CBD does not substitute for delta^9-THC in rats (Vann et al., 2008).

Discriminative stimulus effects of delta^9-THC are pharmacologically specific for marijuana-containing cannabinoids (Balster and Prescott, 1992; Browne and Weissman, 1981; Wiley et al., 1993, 1995). 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.

Central Nervous System Effects

Human Psychological and Behavioral Effects

Psychoactive Effects

Below is a list of the common subjective responses to cannabinoids (Adams and Martin, 1996; Gonzalez, 2007; Hollister 1986, 1988; Institute of Medicine, 1982). According to Maldonado (2002), these responses to marijuana are pleasurable to many humans and are

often associated with drug-seeking and drug-taking. High levels of positive psychoactive effects are associated with increased marijuana use, abuse, and dependence (Scherrer et al., 2009; Zeiger et al., 2010).

1) Disinhibition, relaxation, increased sociability, and talkativeness.
2) Increased merriment and appetite, and even exhilaration at high doses.
3) Enhanced sensory perception, which can generate an increased appreciation of music, art, and touch.
4) Heightened imagination, which can lead to a subjective sense of increased creativity.
5) Initial dizziness, nausea, tachycardia, facial flushing, dry mouth, and tremor.
6) Disorganized thinking, inability to converse logically, time distortions, and short-term memory impairment.
7) Ataxia and impaired judgment, which can impede driving ability or lead to an increase in risk-tasking behavior.
8) Illusions, delusions, and hallucinations that intensify with higher doses.
9) Emotional lability, incongruity of affect, dysphoria, agitation, paranoia, confusion, drowsiness, and panic attacks, which are more common in inexperienced or high-dosed users.

As with many psychoactive drugs, a person's medical, psychiatric, and drug-taking history can influence the individual's response to marijuana. Dose preferences to marijuana occur in that marijuana users prefer higher concentrations of the principal psychoactive substance (1.95 percent delta^9-THC) over lower concentrations (0.63 percent delta^9-THC) (Chait and Burke, 1994). Nonetheless, frequent marijuana users (>100 times of use) were able to identify a drug effect from low-dose delta^9-THC better than occasional users (<10 times of use) while also experiencing fewer sedative effects from marijuana (Kirk and deWit, 1999).

The petitioners contend that many of marijuana's naturally occurring cannabinoids mitigate the psychoactive effects of delta^9-THC, and therefore that marijuana lacks sufficient abuse potential to warrant Schedule I placement, because Marinol, which is in Schedule III, contains only delta^9-THC. This theory has not been demonstrated in controlled studies. Moreover, the concept of abuse potential encompasses all properties of a substance, including its chemistry, pharmacology, and pharmacokinetics, as well as usage patterns and diversion history. The abuse potential of a substance is associated with the repeated or sporadic use of a substance in nonmedical situations for the psychoactive effects the substance produces. These psychoactive effects include euphoria, perceptual and other cognitive distortions, hallucinations, and mood changes. However, as stated above, the abuse potential not only includes the psychoactive effects, but also includes other aspects related to a substance.

DEA's final published rule entitled "Rescheduling of the Food and Drug Administration Approved Product Containing Synthetic Dronabinol [(-)- delta ^{9}-(trans)-Tetrahydrocannabinol] in Sesame Oil and Encapsulated in Soft Gelatin Capsules From Schedule II to Schedule III" (64 FR 35928, July 2, 1999) rescheduled Marinol from Schedule II to Schedule III. The HHS assessment of the abuse potential and subsequent scheduling recommendation compared Marinol to marijuana on different aspects related to abuse

potential. Major differences in formulation, availability, and usage between marijuana and the drug product, Marinol, contribute to their differing abuse potentials.

Hollister and Gillespie (1973) estimated that delta^9-THC by smoking is 2.6 to 3 times more potent than delta^9-THC ingested orally. The intense psychoactive drug effect achieved rapidly by smoking is generally considered to produce the effect desired by the abuser. This effect explains why abusers often prefer to administer certain drugs by inhalation, intravenously, or intranasally rather than orally. Such is the case with cocaine, opium, heroin, phencyclidine, methamphetamine, and delta^9-THC from marijuana (0.1-9.5 percent delta^9-THC range) or hashish (10-30 percent delta^9-THC range) (Wesson and Washburn, 1990). Thus, the delayed onset and longer duration of action for Marinol may be contributing factors limiting the abuse or appeal of Marinol as a drug of abuse relative to marijuana.

The formulation of Marinol is a factor that contributes to differential scheduling of Marinol and marijuana. For example, extraction and purification of dronabinol from the encapsulated sesame oil mixture of Marinol is highly complex and difficult. Additionally, the presence of sesame oil mixture in the formulation may preclude the smoking of Marinol-laced cigarettes.

Additionally, there is a dramatic difference between actual abuse and illicit trafficking of Marinol and marijuana. Despite Marinol's availability in the United States, there have been no significant reports of abuse, diversion, or public health problems due to Marinol. By comparison, 18.9 million American adults report currently using marijuana (SAMHSA, 2013).

In addition, FDA's approval of an NDA for Marinol allowed for Marinol to be rescheduled to Schedule II, and subsequently to Schedule III of the CSA. In conclusion, marijuana and Marinol differ on a wide variety of factors that contribute to each substance's abuse potential. These differences are major reasons distinguishing the higher abuse potential for marijuana and the different scheduling determinations of marijuana and Marinol.

In terms of the petitioners' claim that different cannabinoids present in marijuana mitigate the psychoactive effects of delta^9-THC, only three of the cannabinoids present in marijuana were simultaneously administered with delta^9-THC to examine how the combinations of these cannabinoids such as CBD, cannabichromene (CBC) and cannabinol (CBN) influence delta^9-THC's psychoactive effects. Dalton et al. (1976) observed that smoked administration of placebo marijuana cigarettes containing injections of 0.15mg/kg CBD combined with 0.025mg/kg of delta^9-THC, in a 7:1 ratio of CBD to delta^9-THC, significantly decreased ratings of acute subjective effects and "high" when compared to smoking delta^9-THC alone. In contrast, Ilan et al. (2005) calculated the naturally occurring concentrations of CBC and CBD in a batch of marijuana cigarettes with either 1.8 percent or 3.6 percent delta^9-THC concentration by weight. For each strength of delta^9-THC in marijuana cigarettes, the concentrations of CBC and CBD were classified in groups of either low or high. The study varied the amount of CBC and CBD within each strength of delta^9-THC marijuana cigarettes, with administrations consisting of either low CBC (between 0.1-0.2 percent CBC concentration by weight) and low CBD (between 0.1-0.4 percent CBD concentration by

weight), high CBC (>0.5 percent CBC concentration by weight) and low CBD, or low CBC and high CBD (>1.0 percent CBD concentration by weight). Overall, all combinations scored significantly greater than placebo on ratings of subjective effects, and there was no significant difference between any combinations.

The oral administration of a combination of either 15, 30, or 60 mg CBD with 30 mg delta^9-THC dissolved in liquid (in a ratio of at least 1:2 CBD to delta^9-THC) reduced the subjective effects produced by delta^9-THC alone (Karniol et al., 1974). Additionally, orally administering a liquid mixture combining 1 mg/kg CBD with 0.5 mg/kg of delta^9-THC (ratio of 2:1 CBD to delta^9-THC) decreased scores of anxiety and marijuana drug effect on the Addiction Research Center Inventory (ARCI) compared to delta^9-THC alone (Zuardi et al., 1982). Lastly, oral administration of either 12.5, 25, or 50 mg CBN combined with 25 mg delta^9-THC dissolved in liquid (ratio of at least 1:2 CBN to delta^9-THC) significantly increased subjective ratings of "drugged," "drowsy," "dizzy," and "drunk," compared to delta^9-THC alone (Karniol et al., 1975).

Even though some studies suggest that CBD may decrease some of delta^9-THC's psychoactive effects, the ratios of CBD to delta^9-THC administered in these studies are not present in marijuana used by most people. For example, in one study, researchers used smoked marijuana with ratios of CBD to delta^9-THC naturally present in marijuana plant material and they found out that varying the amount of CBD actually had no effect on delta^9-THC's psychoactive effects (Ilan et al., 2005). Because most marijuana currently available on the street has high amounts of delta^9-THC with low amounts of CBD and other cannabinoids, most individuals use marijuana with low levels of CBD present (Mehmedic et al., 2010). Thus, any possible mitigation of delta^9-THC's psychoactive effects by CBD will not occur for most marijuana users. In contrast, one study indicated that another cannabinoid present in marijuana, CBN, may enhance delta^9-THC's psychoactive effects (Karniol et al., 1975).

Behavioral Impairment

Marijuana induces various psychoactive effects that can lead to behavioral impairment. Marijuana's acute effects can significantly interfere with a person's ability to learn in the classroom or to operate motor vehicles. Acute administration of smoked marijuana impairs performance on learning, associative processes, and psychomotor behavioral tests (Block et al., 1992). Ramaekers et al. (2006a) showed that acute administration of 250 µg/kg and 500 µg/kg of delta^9-THC in smoked marijuana dose-dependently impairs cognition and motor control, including motor impulsivity and tracking impairments (Ramaekers et al., 2006b). Similarly, administration of 290 µg/kg delta^9-THC in a smoked marijuana cigarette resulted in impaired perceptual motor speed and accuracy: two skills which are critical to driving ability (Kurzthaler et al., 1999). Lastly, administration of 3.95 percent delta^9-THC in a smoked marijuana cigarette not only increased disequilibrium measures, but also increased the latency in a task of simulated vehicle braking at a rate comparable to an increase in stopping distance of five feet at 60 mph (Liguori et al., 1998). However, acute administration of marijuana containing 2.1 percent delta^9-THC does not produce "hangover effects" (Chait, 1990).

In addition to measuring the acute effects immediately following marijuana administration, researchers have conducted studies to determine how long behavioral impairments last after abstinence. Some of marijuana's acute effects may not fully resolve until at least one day after the acute psychoactive effects have subsided. 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 that the morning after exposure to 1.8 percent or 3.6 percent smoked delta^9-THC, subjects had minimal residual alterations in subjective or performance measures.

A number of factors may influence marijuana's behavioral effects including the duration of use (chronic or short term), frequency of use (daily, weekly, or occasionally), and amount of use (heavy or moderate). Researchers also have examined how long behavioral impairments last following chronic marijuana use. These studies used self-reported histories of past duration, frequency, and amount of past marijuana use, and administered a variety of performance and cognitive measures at different time points following marijuana abstinence. In chronic marijuana users, behavioral impairments may persist for up to 28 days of abstinence. Solowij et al. (2002) demonstrated that after 17 hours of abstinence, 51 adult heavy chronic marijuana users performed worse on memory and attention tasks than 33 non-using controls or 51 heavy, short-term users. Another study noted that heavy, frequent marijuana users, abstinent for at least 24 hours, performed significantly worse than the controls on verbal memory and psychomotor speed tests (Messinis et al., 2006). Additionally, after at least 1 week of abstinence, young adult frequent marijuana users, aged 18-28, showed deficits in psychomotor speed, sustained attention, and cognitive inhibition (Lisdahl and Price, 2012). Adult heavy, chronic marijuana users showed deficits on memory tests after 7 days of supervised abstinence (Pope et al., 2002). However, when these same individuals were again tested after 28 days of abstinence, they did not show significant memory deficits. The authors concluded, "cannabis-associated cognitive deficits are reversible and related to recent cannabis exposure, rather than irreversible and related to cumulative lifetime use."[3] However, other researchers reported neuropsychological deficits in memory, executive functioning, psychomotor speed and manual dexterity in heavy marijuana users abstinent for 28 days (Bolla et al., 2002). Furthermore, a follow-up study of heavy marijuana users noted decision-making deficits after 25 days of supervised abstinence (Bolla et al., 2005). However, moderate marijuana users did not show decision-making deficits after 25 days of abstinence, suggesting the amount of marijuana use may impact the duration of residual impairment.

The effects of chronic marijuana use do not seem to persist after more than 1 to 3 months of abstinence. After 3 months of abstinence, any deficits observed in IQ, immediate memory, delayed memory, and information-processing speeds following heavy marijuana use compared to pre-drug use scores were no longer apparent (Fried et al., 2005). Marijuana did not appear to have lasting 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). Similarly, following abstinence for a year or more, both light and heavy adult marijuana

[3] In this quotation the term *Cannabis* is used interchangeably for *marijuana*.

users did not show deficits on scores of verbal memory compared to non-using controls (Tait et al., 2011). According to a recent meta-analysis looking at non-acute and long-lasting effects of marijuana use on neurocognitive performance, any deficits seen within the first month following abstinence are generally not present after about 1 month of abstinence (Schreiner and Dunn, 2012).

Another aspect that may be a critical factor in the intensity and persistence of impairment resulting from chronic marijuana use is the age of first use. Individuals with a diagnosis of marijuana misuse or dependence who were seeking treatment for substance use, who initiated marijuana use before the age of 15 years, showed deficits in performance on tasks assessing sustained attention, impulse control, and general executive functioning compared to non-using controls. These deficits were not seen in individuals who initiated marijuana use after the age of 15 years (Fontes et al., 2011). Similarly, heavy, chronic marijuana users who began using marijuana before the age of 16 years had greater decrements in executive functioning tasks than heavy, chronic marijuana users who started using after the age of 16 years and non-using controls (Gruber et al., 2012). Additionally, in a prospective longitudinal birth cohort study of 1,037 individuals, marijuana dependence or chronic marijuana use was associated with a decrease in IQ and general neuropsychological performance compared to pre-marijuana exposure levels in adolescent onset users (Meier et al., 2012). The decline in adolescent-onset user's IQ persisted even after reduction or abstinence of marijuana use for at least 1 year. In contrast, the adult-onset chronic marijuana users showed no significant changes in IQ compared to pre-exposure levels whether they were current users or abstinent for at least 1 year (Meier et al., 2012).

In addition to the age of onset of use, some evidence suggests that the amount of marijuana used may relate to the intensity of impairments. In the above study by Gruber et al. (2012), where early-onset users had greater deficits than late-onset users, the early-onset users reported using marijuana twice as often and using three times as much marijuana per week than the late-onset users. Meier et al. (2012) showed that the deficits in IQ seen in adolescent-onset users increased with the amount of marijuana used. Moreover, when comparing scores for measures of IQ, immediate memory, delayed memory, and information-processing speeds to pre-drug-use levels, the current, heavy, chronic marijuana users showed deficits in all three measures while current, occasional marijuana users did not (Fried et al., 2005).

Behavioral Effects of Prenatal Exposure

Studies with children at different stages of development are used to examine the impact of prenatal marijuana exposure on performance in a series of cognitive tasks. However, many pregnant women who reported marijuana use were more likely to also report use of alcohol, tobacco, and cocaine (Goldschmidt et al., 2008). Thus, with potential exposure to multiple drugs, it is difficult to determine the specific impact of prenatal marijuana exposure.

Most studies assessing the behavioral effects of prenatal marijuana exposure included women who, in addition to using marijuana, also reported using alcohol and tobacco. However, some evidence suggests an association between heavy prenatal marijuana exposure and deficits in some cognitive domains. In both 4-year-old and 6-year-old children, heavy

prenatal marijuana use is negatively associated with performance on tasks assessing memory, verbal reasoning, and quantitative reasoning (Fried and Watkinson, 1987; Goldschmidt et al., 2008). Additionally, heavy prenatal marijuana use is associated with deficits in measures of sustained attention in children at the ages of 6 years and 13–16 years (Fried et al., 1992; Fried, 2002). In 9- to 12-year-old children, prenatal marijuana exposure is negatively associated with executive functioning tasks that require impulse control, visual analysis, and hypothesis (Fried et al., 1998).

Association of Marijuana Use with Psychosis

This analysis evaluates only the evidence for a direct link between prior marijuana use and the subsequent development of psychosis. Thus, this discussion does not consider issues such as whether marijuana's transient effects are similar to psychotic symptoms in healthy individuals or exacerbate psychotic symptoms in individuals already diagnosed with schizophrenia.

Extensive research has been conducted to investigate whether exposure to marijuana is associated with the development of schizophrenia or other psychoses. Although many studies are small and inferential, other studies in the literature use hundreds to thousands of subjects. At present, the available data do not suggest a causative link between marijuana use and the development of psychosis (Minozzi et al., 2010). Numerous large, longitudinal studies show that subjects who used marijuana do not have a greater incidence of psychotic diagnoses compared to those who do not use marijuana (Fergusson et al., 2005; Kuepper et al., 2011; Van Os et al., 2002).

When analyzing the available evidence of the connection between psychosis and marijuana, it is critical to determine whether the subjects in the studies are patients who are already diagnosed with psychosis or individuals who demonstrate a limited number of symptoms associated with psychosis without qualifying for a diagnosis of the disorder. For example, instead of using a diagnosis of psychosis, some researchers relied on non-standard methods of representing symptoms of psychosis including "schizophrenic cluster" (Maremmani et al., 2004), "subclinical psychotic symptoms" (Van Gastel et al., 2012), "pre-psychotic clinical high risk" (Van der Meer et al., 2012), and symptoms related to "psychosis vulnerability" (Griffith-Lendering et al., 2012). These groupings do not conform to the criteria in the Diagnostic and Statistical Manual (DSM-5) or the International Classification of Diseases (ICD-10) for a diagnosis of psychosis. Thus, these groupings are not appropriate for use in evaluating marijuana's impact on the development of actual psychosis. Accordingly, this analysis includes only those studies that use subjects diagnosed with a psychotic disorder.

In the largest study evaluating the link between psychosis and drug use, 274 of the approximately 45,500 Swedish conscripts in the study population (<0.01 percent) received a diagnosis of schizophrenia within the 14-year period following military induction from 1969 to 1983 (Andreasson et al., 1987). Of the conscripts diagnosed with psychosis, 7.7 percent (21 of the 274 conscripts with psychosis) had used marijuana more than 50 times at induction, while 72 percent (197 of the 274 conscripts with psychosis) had never used marijuana. Although high marijuana use increased the relative risk for schizophrenia to 6.0,

the authors note that substantial marijuana use history "accounts for only a minority of all cases" of psychosis (Andreasson et al., 1987). Instead, the best predictor for whether a conscript would develop psychosis was a non-psychotic psychiatric diagnosis upon induction. The authors concluded that marijuana use increased the risk for psychosis only among individuals predisposed to develop the disorder. In addition, a 35-year follow up to this study reported very similar results (Manrique-Garcia et al., 2012). In this follow up study, 354 conscripts developed schizophrenia; of these 354 conscripts, 32 used marijuana more than 50 times at induction (9 percent, an odds ratio of 6.3), while 255 had never used marijuana (72 percent).

Additionally, the conclusion that the impact of marijuana may manifest only in individuals likely to develop psychotic disorders has been shown in many other types of studies. For example, although evidence shows that marijuana use may precede the presentation of symptoms in individuals later diagnosed with psychosis (Schimmelmann et al., 2011), most reports conclude that prodromal symptoms of schizophrenia appear prior to marijuana use (Schiffman et al., 2005). Similarly, a review of the gene-environment interaction model for marijuana and psychosis concluded that some evidence supports marijuana use as a factor that may influence the development of psychosis, but only in those individuals with psychotic liability (Pelayo-Teran et al., 2012).

A similar conclusion was drawn when the prevalence of schizophrenia was modeled against marijuana use across eight birth cohorts in Australia in individuals born between the years 1940 to 1979 (Degenhardt et al., 2003). Although marijuana use increased over time in adults born during the four-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 have tried or continue to use marijuana. However, in individuals with a genetic vulnerability for psychosis, marijuana use may influence the development of psychosis.

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). Some evidence associates the tachycardia produced by delta^9-THC with excitation of the sympathetic and depression of the parasympathetic nervous systems (Malinowska et al., 2012). During chronic marijuana ingestion, a tolerance to tachycardia develops (Malinowska et al., 2012).

However, prolonged delta^9-THC ingestion produces bradycardia and hypotension (Benowitz and Jones, 1975). Plant-derived cannabinoids and endocannabinoids elicit hypotension and bradycardia via activation of peripherally-located CB_1 receptors (Wagner et al., 1998). Specifically, 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 (Pacher et al., 2006). In humans, tolerance can develop to orthostatic hypotension (Jones,

2002; Sidney, 2002) possibly related to plasma volume expansion, but tolerance does not develop to the supine hypotensive effects (Benowitz and Jones, 1975). Additionally, electrocardiographic changes are minimal, even after large cumulative doses of delta^9-THC are administered. (Benowitz and Jones, 1975)

Marijuana smoking by individuals, particularly those with some degree of coronary artery or cerebrovascular disease, poses risks such as increased cardiac work, catecholamines and carboxyhemoglobin, myocardial infarction, and postural hypotension (Benowitz and Jones, 1981; Hollister, 1988; Mittleman et al., 2001; Malinowska et al., 2012).

Respiratory Effects

After acute exposure to marijuana, transient bronchodilation is the most typical respiratory effect (Gong et al., 1984). A recent 20-year longitudinal study with over 5,000 individuals collected information on the amount of marijuana use and pulmonary function data at years 0, 2, 5, 10, and 20 (Pletcher et al., 2012). Among the more than 5,000 individuals who participated in the study, almost 800 of them reported current marijuana use but not tobacco use at the time of assessment. Pletcher et al. (2012) found that the occasional use of marijuana is not associated with decreased pulmonary function. However, some preliminary evidence suggests that heavy marijuana use may be associated with negative pulmonary effects (Pletcher et al., 2012). Long-term use of marijuana can lead to chronic cough and increased sputum, as well as an increased frequency of chronic bronchitis and pharyngitis. In addition, 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).

Evidence regarding marijuana smoking leading to cancer is inconsistent, as some studies suggest a positive correlation while others do not (Lee and Hancox, 2011; Tashkin, 2005). Several lung cancer cases have been reported in young marijuana users with no tobacco smoking history 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 a large study with 1,650 subjects, a positive association was not found between marijuana and lung cancer (Tashkin et al., 2006). This finding remained true, regardless of the extent of marijuana use, when controlling for tobacco use and other potential confounding variables. Overall, new evidence suggests that the effects of marijuana smoking on respiratory function and carcinogenicity differ from those of tobacco smoking (Lee and Hancox, 2011).

Endocrine System

Experimental marijuana administration to humans does not consistently alter many 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 (Cone et al., 1986). However, two later studies showed no changes in hormones. Male subjects experimentally exposed to smoked delta^9-THC (18 mg/marijuana cigarette) or oral delta^9-THC (10 mg three times per day for 3 days and on the morning of the fourth day) showed no changes in plasma adrenocorticotropic hormone (ACTH), cortisol, prolactin,

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). Additionally, chronic marijuana use did not affect serum levels of thyrotropin, thyroxine, and triiodothyronine (Bonnet, 2013). However, in a double-blind, placebo-controlled, randomized clinical trial of HIV-positive men, smoking marijuana dose-dependently increased plasma levels of ghrelin and leptin, and decreased plasma levels of peptide YY (Riggs et al., 2012).

The effects of marijuana on female reproductive system functionality differ between humans and animals. In monkeys, delta^9-THC administration suppressed ovulation (Asch et al., 1981) and reduced progesterone levels (Almirez et al., 1983). However, in women, smoked marijuana did not alter hormone levels or the menstrual cycle (Mendelson and Mello, 1984). Brown and Dobs (2002) suggest that the development of tolerance in humans may be the cause of the discrepancies between animal and human hormonal response to cannabinoids.

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). Although acute delta^9-THC presence releases corticosterone, tolerance develops in rats with chronic administration (Eldridge et al., 1991).

Some studies support a possible association between frequent, long-term marijuana use and increased risk of testicular germ cell tumors (Trabert et al., 2011). On the other hand, 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 cells, as well as decreases the expression of androgen receptors and prostate-specific antigens (Sarfaraz et al., 2005).

Immune System

Cannabinoids affect the immune system in many different ways. Synthetic, natural, and endogenous cannabinoids often cause different effects in a dose-dependent biphasic manner (Croxford and Yamamura, 2005; Tanasescu and Constantinescu, 2010).

Studies in humans and animals give conflicting results about cannabinoid effects on immune functioning in subjects with compromised immune systems. Abrams et al. (2003) investigated marijuana's effect on immunological functioning in 62 AIDS patients taking protease inhibitors. Subjects received one of the following three times a day: a smoked marijuana cigarette containing 3.95 percent delta^9-THC, an oral tablet containing delta^9-THC (2.5 mg oral dronabinol), or an oral placebo. The results showed no changes in CD4+ and CD8+ cell counts, HIV RNA levels, or protease inhibitor levels between groups. Thus, the use of cannabinoids showed no short-term adverse virologic effects in individuals with compromised immune systems. However, these human data contrast with data generated in immunodeficient mice, which demonstrated 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

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

Chemistry

Marijuana is one of the common names of *Cannabis sativa* L. in the family Cannabaceae. *Cannabis* is one of the oldest cultivated crops, providing a source of fiber, food, oil, and drug. Botanists still debate whether *Cannabis* should be considered as a single (The Plant List, 2010) or three species, i.e., *C. sativa, C. indica,* and *C. ruderalis* (Hillig, 2005). Specifically, marijuana is developed as sativa and indica cultivated varieties (strains) or various hybrids.

The petition defines marijuana as including all *Cannabis* cultivated strains. Different marijuana samples derived from various cultivated strains may have very different chemical constituents including delta^{9}-THC and other cannabinoids (Appendino et al., 2011). As a consequence, marijuana products from different strains will have different safety, biological, pharmacological, and toxicological profiles. Thus, all *Cannabis* strains cannot be considered together because of the varying chemical constituents between strains.

Marijuana contains numerous naturally occurring constituents including cannabinoids. Overall, various *Cannabis* strains contain more than 525 identified natural constituents. Among those constituents, the most important ones are the 21 (or 22) carbon terpenoids found in the plant, as well as their carboxylic acids, analogues, and transformation products, known as cannabinoids (Agurell et al., 1984, 1986; Mechoulam, 1973; Appendino et al., 2011). Thus far, more than 100 compounds classified as cannabinoids have been characterized (ElSohly and Slade, 2005; Radwan, ElSohly et al., 2009; Appendino et al. 2011).

Cannabinoids primarily exist in *Cannabis*, and published data suggest that most major cannabinoid compounds occurring naturally have been chemically identified. New and minor cannabinoids and other new compounds are continuously being characterized (Pollastro et al., 2011). So far, only two cannabinoids (cannabigerol and its corresponding acid) have been obtained from a non-*Cannabis* source. A South African *Helichrysum* (*H. umbraculigerum*) accumulates these compounds (Appendino et al. 2011).

Among the cannabinoids found in marijuana, delta^{9}-THC (alternate name delta^{1}-THC) and delta-8-tetrahydrocannabinol (delta^{8}-THC, alternate name delta^{6}-THC) produce marijuana's characteristic psychoactive effects. Because delta^{9}-THC is more abundant than delta^{8}-THC,

marijuana's psychoactivity is largely attributed to the former. Only a few varieties of marijuana analyzed contain delta^8-THC at significant amounts (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 (-)-delta9-(trans)-tetrahydrocannabinol. The (-)-trans isomer of delta^9-THC is pharmacologically 6–100 times more potent than the (+)-trans isomer (Dewey et al., 1984).

Other cannabinoids present in marijuana include CBD, CBC, and CBN. CBD, a major cannabinoid of marijuana, is insoluble in water and lipid-soluble. Chemically, CBD is 2-[(1R,6R)-3-methyl-6-prop-1-en-2-ylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol. CBD does not have cannabinol-like psychoactivity (Adams and Martin, 1996; Agurell et al., 1984, 1986; Hollister, 1986). CBC is another major cannabinoid in marijuana. Chemically, CBC is 2-methyl-2-(4-methylpent-3-enyl)-7-pentyl-5-chromenol. CBN, a major metabolite of delta^9-THC, is also a minor naturally-occurring cannabinoid with weak psychoactivity. Chemically, CBN is 6,6,9-trimethyl-3-pentyl-benzo[c]chromen-1-ol.

Different marijuana samples derived from various cultivated strains may differ in chemical constituents including delta^9-THC and other cannabinoids (Appendino et al. 2011). As a consequence, marijuana products from different strains may have different safety, biological, pharmacological, and toxicological profiles. In addition to differences between cultivated strains, the concentration of delta^9-THC and other cannabinoids in marijuana may vary with growing conditions and processing after harvest. In addition to genetic differences among *Cannabis* species, the plant parts collected—for example, flowers, leaves, and stems—can influence marijuana's potency, quality, and purity (Adams and Martin, 1996; Agurell et al., 1984; Mechoulam, 1973). All these variations produce marijuana with potencies, as indicated by cannabinoid content, on average from as low as 1-2 percent to as high as 17 percent.

Overall, these variations in the concentrations of cannabinoids and other chemical constituents in marijuana complicate the interpretation of clinical data using marijuana. The lack of consistent concentrations of delta^9-THC and other substances in marijuana from diverse sources makes interpreting the effect of different marijuana constituents difficult. In addition to different cannabinoid concentrations having different pharmacological and toxicological profiles, the non-cannabinoid components in marijuana, such as other terpenoids and flavonoids, might also contribute to the overall pharmacological and toxicological profiles of various marijuana strains and products derived from those strains.

The term marijuana is often used to refer to a mixture of the dried flowering tops and leaves from *Cannabis*. Marijuana in this limiting definition is one of three major derivatives sold as separate illicit products, which also include hashish and hash oil. According to the DEA, *Cannabis sativa* is the primary species of *Cannabis* currently marketed illegally in the United States.

Marijuana can vary in cannabinoid content and potency (Agurell et al., 1984, 1986; Mechoulam 1973, Cascini et al., 2012). In the usual mixture of leaves and stems distributed

as marijuana, the concentration of delta^9-THC averages over 12 percent by weight. However, specially grown and selected marijuana can contain 15 percent or greater delta^9-THC (Appendino et al. 2011). Thus, a 1-gram marijuana cigarette might contain delta^9-THC in a range from as little as 3 milligrams to as much as 150 milligrams or more. Additionally, a recent systematic review and meta-analysis found that marijuana's delta^9-THC content has increased significantly from 1979-2009 (Cascini et al., 2012). In addition to smoking marijuana, individuals ingest marijuana through food made with butter or oil infused with marijuana and its extracts. These marijuana butters are generally made by adding marijuana to butter and heating it. The resultant butter is then used to cook a variety of foods. There are no published studies measuring the concentrations of cannabinoids in these marijuana food products.

Hashish consists of the dried and compressed cannabinoid-rich resinous material of *Cannabis* and comes in a variety of forms (e.g. balls and cakes). Individuals may break off pieces, place it into a pipe and smoke it. DEA reports that cannabinoid content in hashish averages six percent (DEA, 2005). With the development and cultivation of more high potency *Cannabis* strains, the average cannabinoid content in hashish will likely increase.

Hash oil is produced by solvent extraction of the cannabinoids from plant material. The extract's color and odor vary, depending on the solvent type used. Hash oil is a viscous brown- or amber-colored liquid containing approximately 50 percent cannabinoids. One or two drops of the liquid placed on a cigarette purportedly produce the equivalent of a single marijuana cigarette (DEA, 2005).

In conclusion, marijuana has hundreds of cultivars containing variable concentrations of delta^9-THC, cannabinoids, and other compounds. Thus, marijuana is not a single chemical with a consistent and reproducible chemical profile or predictable and consistent clinical effects. A guidance for industry, entitled *Botanical Drug Products,*[4] provides information on the approval of botanical drug products. To investigate marijuana for medical use in a manner acceptable as support for marketing approval under an NDA, clinical studies under an IND of consistent batches of a particular marijuana product for particular disease indications should be conducted. In addition, information and data regarding the marijuana product's chemistry, manufacturing and control, pharmacology, and animal toxicology data, among others must be provided and meet the requirements for new drug approval (See 21 CFR 314.50).

Human Pharmacokinetics

Marijuana can be taken in a variety of formulations by multiple routes of administration. Individuals smoke marijuana as a cigarette, weighing between 0.5 and 1.0 gram, or in a pipe. Additionally, individuals take marijuana orally in foods or as an extract in ethanol or other solvents. More recently, access to vaporizers provides another means for abusers to inhale marijuana,

[4] This guidance is available on the Internet at http://www.fda.gov/Drugs/default.htm under Guidance (Drugs).

The absorption, metabolism, and pharmacokinetic profile of delta^9-THC, cannabinoids, and drug products containing delta^9-THC vary with route of administration and formulation (Adams and Martin, 1996; Agurell et al., 1984, 1986).

Pharmacokinetics of Smoked Administration of Cannabinoids

Characterization of the pharmacokinetics of delta^9-THC and other cannabinoids from smoked marijuana is difficult because a subject's smoking behavior during an experiment varies (Agurell et al., 1986; Herning et al., 1986; Huestis et al., 1992a). 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 minimize undesired effects. For example, under naturalistic conditions, users hold marijuana smoke in their lungs for an extended period of time which causes prolonged absorption and increases psychoactive effects. The effect of experience in the psychological response may explain why delta^9-THC venous blood levels correlate poorly with intensity of effects and intoxication level (Agurell et al. 1986; Barnett et al. 1985; Huestis et al., 1992a). Puff and inhalation volumes should be recorded in studies as the concentration (dose) of cannabinoids administered can vary at different stages of smoking.

Smoked marijuana results in absorption of delta^9-THC in the form of an aerosol within seconds. Psychoactive effects occur immediately following absorption, with mental and behavioral effects measurable for up to 6 hours (Grotenhermen, 2003; Hollister 1986, 1988). Delta^9-THC is delivered to the brain rapidly and efficiently as 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 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. An individual's experience and technique with smoking marijuana also determines the dose absorbed (Herning et al., 1986; Johansson et al., 1989). After smoking, delta^9-THC venous levels decline precipitously within minutes, and continue to go down to about 5 to 10 percent of the peak level within an hour (Agurell et al., 1986, Huestis et al., 1992a, 1992b).

Pharmacokinetics for Oral Administration of Cannabinoids

After oral administration of delta^9-THC or marijuana, the onset of effects starts within 30 to 90 minutes, reaches its peak after 2 to 3 hours and then remains for 4 to 12 hours (Grotenhermen, 2003; Adams and Martin, 1996; Agurell et al., 1984, 1986). Due to the delay in onset of effects, users have difficulty in titrating oral delta^9-THC doses compared to smoking marijuana. Oral bioavailability of delta^9-THC, whether pure or in marijuana, is low and extremely variable, ranging between 5 and 20 percent (Agurell et al., 1984, 1986). Following oral administration of radioactive-labeled delta^9-THC, delta^9-THC plasma levels are low relative to plasma levels after smoking or intravenous administration. Inter- and

intra-subject variability occurs even with repeated dosing 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.

Cannabinoid Metabolism and Excretion

Cannabinoid metabolism is complex. Delta^9-THC is metabolized via microsomal hydroxylation to both active and inactive metabolites (Lemberger et al., 1970, 1972a, 1972b; Agurell et al., 1986; Hollister, 1988). The primary active metabolite of delta^9-THC following oral ingestion is 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.

Plasma clearance of delta^9-THC approximates hepatic blood flow at about 950 ml/min or greater. The rapid disappearance of delta^9-THC from blood is largely due to redistribution to other tissues in the body, rather than to metabolism (Agurell et al., 1984, 1986). Metabolism in most tissues is relatively slow or absent. Slow release of delta^9-THC and other cannabinoids from tissues and subsequent metabolism results in a long elimination half-life. The terminal half-life of delta^9-THC ranges from approximately 20 hours to as long as 10 to 13 days, though reported estimates vary as expected with any slowly cleared substance and the use of assays with variable sensitivities (Hunt and Jones, 1980). 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. 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 in urine tests for earlier marijuana use.

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 non-conjugated metabolites. Frequent and infrequent marijuana users metabolize delta^9-THC similarly (Agurell et al., 1986).

Status of Research into the Medical Uses for Marijuana

State-level public initiatives, including laws and referenda in support of the medical use of marijuana, have generated interest in the medical community and the need for high quality clinical investigation as well as comprehensive safety and effectiveness data. In order to address the need for high quality clinical investigations, the state of California established the Center for Medicinal Cannabis Research (CMCR, www.cmcr.ucsd.edu) in 2000 "in response to scientific evidence for therapeutic possibilities of cannabis[5] and local legislative initiatives in favor of compassionate use" (Grant, 2005). State legislation establishing the CMCR called for high quality medical research that would "enhance understanding of the efficacy and adverse effects of marijuana as a pharmacological agent," but stressed the project

[5] In this quotation the term cannabis is interchangeable with marijuana

"should not be construed as encouraging or sanctioning the social or recreational use of marijuana." The CMCR funded many of the published studies on marijuana's potential use for treating multiple sclerosis, neuropathic pain, appetite suppression and cachexia. However, aside from the data produced by CMCR, no state-level medical marijuana laws have produced scientific data on marijuana's safety and effectiveness.

FDA approves medical use of a drug following a submission and review of an NDA or BLA. The FDA has not approved any drug product containing marijuana for marketing. Even so, results of small clinical exploratory studies have been published in the current medical literature. Many studies describe human research with marijuana in the United States under FDA-regulated IND applications.

However, FDA approval of an NDA is not the only means through which a drug can have a currently accepted medical use in treatment in the United States. In general, a drug may have a "currently accepted medical use" in treatment in the United States if the drug meets a five-part test. Established case law (Alliance for Cannabis Therapeutics v. DEA, 15 F.3d 1131, 1135 (D.C. Cir. 1994)) upheld the Administrator of DEA's application of the five-part test to determine whether a drug has a "currently accepted medical use." The following describes the five elements that characterize "currently accepted medical use" for a drug[6]:

i. the drug's chemistry must be known and reproducible

"The substance's chemistry must be scientifically established to permit it to be reproduced into dosages which can be standardized. The listing of the substance in a current edition of one of the official compendia, as defined by section 201(j) of the Food, Drug and Cosmetic Act, 21 U.S.C. 321(j), is sufficient to meet this requirement."

ii. there must be adequate safety studies

"There must be adequate pharmacological and toxicological studies, done by all methods reasonably applicable, on the basis of which it could fairly and responsibly be concluded, by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, that the substance is safe for treating a specific, recognized disorder."

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

"There must be adequate, well-controlled, well-designed, well-conducted, and well-documented studies, including clinical investigations, by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, on the basis of which it could be fairly and responsibly concluded by such experts that the substance will have the intended effect in treating a specific, recognized disorder."

[6] 57 FR 10499, 10504-06 (March 26, 1992).

iv. the drug must be accepted by qualified experts

"The drug has a New Drug Application (NDA) approved by the Food and Drug Administration, pursuant to the Food, Drug and Cosmetic Act, 21 U.S.C. 355. Or, a consensus of the national community of experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, accepts the safety and effectiveness of the substance for use in treating a specific, recognized disorder. A material conflict of opinion among experts precludes a finding of consensus." and

v. the scientific evidence must be widely available.

"In the absence of NDA approval, information concerning the chemistry, pharmacology, toxicology, and effectiveness of the substance must be reported, published, or otherwise widely available, in sufficient detail to permit experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, to fairly and responsibly conclude the substance is safe and effective for use in treating a specific, recognized disorder."

Marijuana does not meet any of the five elements necessary for a drug to have a "currently accepted medical use."

Firstly, the chemistry of marijuana, as defined in the petition, is not reproducible in terms of creating a standardized dose. The petition defines marijuana as including all *Cannabis* cultivated strains. Different marijuana samples derived from various cultivated strains may have very different chemical constituents including delta^9-THC and other cannabinoids (Appendino et al., 2011). As a consequence, marijuana products from different strains will have different safety, biological, pharmacological, and toxicological profiles. Thus, when considering all *Cannabis* strains together, because of the varying chemical constituents, reproducing consistent standardized doses is not possible. Additionally, smoking marijuana currently has not been shown to allow delivery of consistent and reproducible doses. However, if a specific *Cannabis* strain is grown and processed under strictly controlled conditions, the plant chemistry may be kept consistent enough to produce reproducible and standardized doses.

As to the second and third criteria, there are neither adequate safety studies nor adequate and well-controlled studies proving marijuana's efficacy. To support the petitioners' assertion that marijuana has accepted medical use, the petitioners cite the American Medical Association's (AMA) 2009 report entitled "Use of Cannabis for Medicinal Purposes." The petitioners claim the AMA report is evidence the AMA accepts marijuana's safety and efficacy. However, the 2009 AMA report clarifies that the report "should not be viewed as an endorsement of state-based medical cannabis programs, the legalization of marijuana, or

that scientific evidence on the therapeutic use of cannabis meets the same and current standards for a prescription drug product."[7]

Currently, no published studies conducted with marijuana meet the criteria of an adequate and well-controlled efficacy study. The criteria for an adequate and well-controlled study for purposes of determining the safety and efficacy of a human drug are defined under the Code of Federal Regulations (CFR) in 21 CFR 314.126. In order to assess this element, FDA conducted a review of clinical studies published and available in the public domain before February, 2013. Studies were identified through a search of PubMed[8] for articles published from inception to February 2013, for randomized controlled trials using marijuana to assess marijuana's efficacy in any therapeutic indication. Additionally, the review included studies identified through a search of bibliographic references in relevant systematic reviews and identified studies presenting original research in any language. Selected studies needed to be placebo-controlled and double-blinded. Additionally, studies needed to encompass administered marijuana plant material. There was no requirement for any specific route of administration, nor any age limits on study subjects. Studies were excluded that used placebo marijuana supplemented by the addition of specific amounts of THC or other cannabinoids. Additionally, studies administering marijuana plant extracts were excluded.

The PubMed search yielded a total of 566 abstracts of scientific articles. Of these abstracts, a full-text review was conducted with 85 papers to assess eligibility. Of the studies identified through the search of the references and the 566 abstracts from the PubMed search, only 11 studies met all the criteria for selection (Abrams et al., 2007; Corey-Bloom et al., 2012; Crawford and Merritt, 1979; Ellis et al., 2009; Haney et al., 2005; Haney et al., 2007; Merritt et al., 1980; Tashkin et al., 1974; Ware et al., 2010; Wilsey et al., 2008; Wilsey et al., 2013). These 11 studies were published between 1974 and 2013. Ten of these studies were conducted in the United States and one study was conducted in Canada. The identified studies examine the effects of smoked and vaporized marijuana for the indications of chronic neuropathic pain, spasticity related to Multiple Sclerosis (MS), appetite stimulation in human immunodeficiency virus (HIV) patients, glaucoma, and asthma. All studies used adult subjects.

The 11 identified studies were individually evaluated to determine if they successfully meet accepted scientific standards. Specifically, they were evaluated on study design including subject selection criteria, sample size, blinding techniques, dosing paradigms, outcome measures, and the statistical analysis of the results. The analysis relied on published studies, thus information available about protocols, procedures, and results were limited to documents published and widely available in the public domain. The review found that all 11 studies that examined effects of inhaled marijuana do not currently prove efficacy of marijuana in any therapeutic indication based on a number of limitations in their study design; however, they may be considered proof of concept studies. Proof of concept studies provide preliminary evidence on a proposed hypothesis involving a drug's effect. For drugs under development, the effect often relates to a short-term clinical outcome being

[7] In this quotation the term cannabis is used interchangeably for marijuana.
[8] The following search strategy was used, "(cannabis OR marijuana) AND (therapeutic use OR therapy) AND (RCT OR randomized controlled trial OR "systematic review" OR clinical trial OR clinical trials) NOT ("marijuana abuse"[Mesh] OR addictive behavior OR substance related disorders)."

investigated. Proof of concept studies often serve as the link between preclinical studies and dose ranging clinical studies. Thus, proof of concept studies generally are not sufficient to prove efficacy of a drug because they provide only preliminary information about the effects of a drug.

In addition to the lack of published adequate and well-controlled efficacy studies proving efficacy, the criteria for adequate safety studies has also not been met. Importantly, in its discussion of the five-part test used to determine whether a drug has a "currently accepted medical use," DEA said, "No drug can be considered safe in the abstract. Safety has meaning only when judged against the intended use of the drug, its known effectiveness, its known and potential risks, the severity of the illness to be treated, and the availability of alternative remedies" (57 FR 10504). 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 side effects are outweighed by the drug product's potential benefits for a particular indication. Thus, contrary to the petitioner's assertion that marijuana has accepted safety, in the absence of an accepted therapeutic indication which can be weighed against marijuana's risks, marijuana does not satisfy the element for having adequate safety studies such that experts may conclude that it is safe for treating a specific, recognized disorder.

The fourth of the five elements for determining "currently accepted medical use" requires that the national community of experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, accepts the safety and effectiveness of the substance for use in treating a specific, recognized disorder. A material conflict of opinion among experts precludes a finding of consensus. Medical practitioners who are not experts in evaluating drugs are not qualified to determine whether a drug is generally recognized as safe and effective or meets NDA requirements (57 FR 10499, 10505).

There is no evidence that there is a consensus among qualified experts that marijuana is safe and effective for use in treating a specific, recognized disorder. As discussed above, there are not adequate scientific studies that show marijuana is safe and effective in treating a specific, recognized disorder. In addition, there is no evidence that a consensus of qualified experts have accepted the safety and effectiveness of marijuana for use in treating a specific, recognized disorder. Although medical practitioners are not qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, we also note that the AMA's report, entitled "Use of Cannabis for Medicinal Purposes," does not accept that marijuana currently has accepted medical use. Furthermore, based on the above definition of a "qualified expert", who is an individual qualified by scientific training and experience to evaluate the safety and effectiveness of a drug, state-level medical marijuana laws do not provide evidence of a consensus among qualified experts that marijuana is safe and effective for use in treating a specific, recognized disorder.

As to the fifth part of the test, which requires that information concerning the chemistry, pharmacology, toxicology, and effectiveness of marijuana to be reported in sufficient detail, the scientific evidence regarding all of these aspects is not available in sufficient detail to allow adequate scientific scrutiny. Specifically, the scientific evidence regarding marijuana's

chemistry in terms of a specific *Cannabis* strain that could produce standardized and reproducible doses is not currently available.

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. Yet, as stated above, currently marijuana does not have any accepted medical use, even under conditions where its use is severely restricted.

In conclusion, to date, research on marijuana's medical use has not progressed to the point where marijuana is 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

Under the fourth factor, the Secretary must consider the history and current pattern of marijuana abuse. A variety of sources provide data necessary to assess abuse patterns and trends of marijuana. The data indicators of marijuana use include the NSDUH, MTF, DAWN, and TEDS. The following briefly describes each data source, and summarizes the data from each source.

National Survey on Drug Use and Health (NSDUH)[9]

According to 2012 NSDUH[10] data, the most recent year with complete data, the use of illicit drugs, including marijuana, is increasing. The 2012 NSDUH estimates that 23.9 million individuals over 12 years of age (9.2 percent of the U.S. population) currently use illicit drugs, which is an increase of 4.8 million individuals from 2004 when 19.1 million individuals (7.9 percent of the U.S. population) were current illicit drug users. NSDUH reports marijuana as the most commonly used illicit drug, with 18.9 million individuals (7.3 percent of the U.S. population) currently using marijuana in 2012. This represents an increase of 4.3 million individuals from 2004, when 14.6 million individuals (6.1 percent of the U.S. population) were current marijuana users.

The majority of individuals who try marijuana at least once in their lifetime do not currently use marijuana. The 2012 NSDUH estimates that 111.2 million individuals (42.8 percent of the U.S. population) have used marijuana at least once in their lifetime. Based on this estimate and the estimate for the number of individuals currently using marijuana, approximately 16.9 percent of those who have tried marijuana at least once in their lifetime

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[9] NSDUH provides national estimates of the prevalence and incidence of illicit drug, alcohol and tobacco use in the United States. NSDUH is an annual study conducted by SAMHSA. Prior to 2002, the database was known as the National Household Survey on Drug Abuse (NHSDA). NSDUH utilizes a nationally representative sample of United States civilian, non-institutionalized population aged 12 years 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. The survey identifies whether an individual used a drug within a specific time period, but does not identify the amount of the drug used on each occasion. NSDUH defines "current use" as having used the substance within the month prior to the study.

[10] 2013; http://www.samhsa.gov/data/NSDUH.aspx

currently use marijuana; conversely, 83.1 percent do not currently use marijuana. In terms of the frequency of marijuana use, an estimated 40.3 percent of individuals who used marijuana in the past month used marijuana on 20 or more days within the past month. This amount corresponds to an estimated 7.6 million individuals who used marijuana on a daily or almost daily basis.

Some characteristics of marijuana users are related to age, gender, and criminal justice system involvement. In observing use among different age cohorts, the majority of individuals who currently use marijuana are shown to be between the ages of 18-25, with 18.7 percent of this age group currently using marijuana. In the 26 and older age group, 5.3 percent of individuals currently use marijuana. Additionally, in individuals aged 12 years and older, males reported more current marijuana use than females.

NSDUH includes a series of questions aimed at assessing the prevalence of dependence and abuse of different substances in the past 12 months.[11] In 2012, marijuana was the most common illicit drug reported by individuals with past year dependence or abuse. An estimated 4.3 million individuals meet the NSDUH criteria for marijuana dependence or abuse in 2012. The estimated rates and number of individuals with marijuana dependence or abuse has remained similar from 2002 to 2012. In addition to data on dependence and abuse, NSDUH includes questions aimed at assessing treatment for a substance use problem.[12] In 2012, an estimated 957,000 persons received treatment for marijuana use during their most recent treatment in the year prior to the survey.

Monitoring the Future (MTF)[13]

According to MTF,[14] rates of marijuana and illicit drug use declined for all three grades from 2005 through 2007. However, starting around 2008, rates of annual use of illicit drugs and

[11] "These questions are used to classify persons as dependent on or abusing specific substances based on criteria specified in the *Diagnostic and Statistical Manual of Mental Disorder*, 4th edition (DSM-IV). The questions related to dependence ask about health and emotional problems associated with substance use, unsuccessful attempts to cut down on use, tolerance, withdrawal, reducing other activities to use substances, spending a lot of time engaging in activities related to substance use, or using the substance in greater quantities or for longer time than intended. The questions on abuse ask about problems at work, home, and school; problems with family or friends; physical danger; and trouble with the law due to substance use. Dependence is considered to be a more severe substance use problem than abuse because it involves the psychological and physiological effects of tolerance and withdrawal." (NSDUH, 2013)

[12] "Estimates... refer to treatment received for illicit drug or alcohol use, or for medical problems associated with the use of illicit drugs or alcohol. This includes treatment received in the past year at any location, such as a hospital (inpatient), rehabilitation facility (outpatient or inpatient), mental health center, emergency room, private doctor's office, prison or jail, or a self-help group, such as Alcoholics Anonymous or Narcotics Anonymous." (NSDUH, 2013).

[13] Monitoring the Future is a national survey that tracks drug use prevalence and trends among adolescents in the United States. MTF is reported annually by the Institute for Social Research at the University of Michigan under a grant from NIDA. Every spring, MTF surveys 8th, 10th, and 12th graders in randomly selected U.S. schools. MTF has been conducted since 1975 for 12th graders and since 1991 for 8th and 10th graders. The MTF survey presents data in terms of prevalence among the sample interviewed. For 2012, the latest year with complete data, the sample sizes were 15,200 – 8th graders; 13,300 – 10th graders; and 13,200 – 12th graders. In all, a total of about 41,700 students of 389 schools participated in the 2013 MTF.

[14] 2013; http://www.monitoringthefuture.org/index.html

marijuana increased through 2013 for all three grades. Marijuana remained the most widely used illicit drug during all time periods. The prevalence of annual and past month marijuana use in 10th and 12th graders in 2013 is greater than in 2005. Table 1 lists the lifetime, annual, and monthly prevalence rates of various drugs for 8th, 10th and 12th graders in 2013.

Table 1: Trends in lifetime, annual, and monthly prevalence of use of various drugs for eighth, tenth, and twelfth graders. Percentages represent students in survey responding that they had used a drug at least once in their lifetime, in the past year, or in the past 30 days.

	Lifetime			Annual			30-Day		
	2011	2012	2013	2011	2012	2013	2011	2012	2013
Any illicit Drug (a)									
8th Grade	20.1	18.5	20.3	14.7	13.4	14.9	8.5	7.7	8.5
10th Grade	37.7	36.8	38.8	31.1	30.1	31.8	19.2	18.6	19.4
12th Grade	49.9	49.1	50.4	40.0	39.7	40.3	25.2	25.2	25.5
Marijuana/Hashish									
8th Grade	16.4	15.2	16.5	12.5	11.4	12.7	7.2	6.5	7.0
10th Grade	34.5	33.8	35.8	28.8	28.0	29.8	17.6	17.0	18.0
12th Grade	45.5	45.2	45.5	36.4	36.4	36.4	22.6	22.9	22.7

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 narcotics use other than heroin, amphetamines, sedatives (barbiturates), or tranquilizers not under a doctor's orders. For 8th and 10th graders only: the use of narcotics other than heroin and sedatives (barbiturates) was excluded.

Drug Abuse Warning Network (DAWN)[15]

Importantly, many factors can influence the estimates of ED visits, including trends in overall use of a substance as well as trends in the reasons for ED usage. For instance, some drug users may visit EDs for life-threatening issues while others may visit to seek care for detoxification because they needed certification before entering treatment. Additionally, DAWN data do not distinguish the drug responsible for the ED visit from other drugs that may have been used concomitantly. As stated in a DAWN report, "Since marijuana/hashish is frequently present in combination with other drugs, the reason for the ED visit may be more relevant to the other drug(s) involved in the episode."

For 2011, DAWN[16] estimates a total of 5,067,374 (95 percent confidence interval [CI]: 4,616,753 to 5,517,995) drug-related ED visits from the entire United States. Of these, approximately 2,462,948 ([CI]: 2,112,868 to 2,813,028) visits involved drug misuse or abuse.

[15] DAWN is a national probability survey of the U.S. hospitals with ED designed to obtain information on drug-related ED visits. DAWN is sponsored by SAMHSA. The DAWN system provides information on the health consequences of drug use in the United States, as manifested by drug-related visits to ED. The ED data from a representative sample of hospital emergency departments are weighted to produce national estimates. Importantly, DAWN data and estimates, starting in 2004, are not comparable to those for prior years because of vast changes in the methodology used to collect the data. Furthermore, estimates for 2004 are the first to be based on a redesigned sample of hospitals, which ended in 2011.

[16] 2011; http://www.samhsa.gov/data/dawn.aspx

During the same period, DAWN estimates that 1,252,500 (CI: 976,169 to 1,528,831) drug-related ED visits involved illicit drugs. Thus, over half of all drug-related ED visits associated with drug misuse or abuse involved an illicit drug. For ED visits involving illicit drugs, 56.3 percent involved multiple drugs while 43.7 percent involved a single drug.

Marijuana was involved in 455,668 ED visits (CI: 370,995 to 540,340), while cocaine was involved in 505,224 (CI: 324,262 to 686,185) ED visits, heroin was involved in 258,482 (CI: 205,046 to 311,918) ED visits and stimulants including amphetamine and methamphetamine were involved in 159,840 (CI: 100,199 to 219,481) ED visits. Other illicit drugs, such as PCP, MDMA, GHB and LSD were much less frequently associated with ED visits. The number of ED visits involving marijuana has increased by 62 percent since 2004.

Marijuana-related ED visits were most frequent among young adults and minors. Individuals under the age of 18 accounted for 13.2 percent of these marijuana-related visits, whereas this age group accounted for approximately 1.2 percent of ED visits involving cocaine, and less than 1 percent of ED visits involving heroin. However, the age group with the most marijuana-related ED visits was between 25 and 29 years old. Yet, because populations differ between age groups, a standardized measure 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 (443.8 ED visits per 100,000) and for patients aged 21 to 24 (446.9 ED visits per 100,000).

While DAWN provides estimates for ED visits associated with the use of medical marijuana for 2009-2011, the validity of these estimates is questionable. Because the drug is not approved by the FDA, reporting medical marijuana may be inconsistent and reliant on a number of factors including whether the patient self-reports the marijuana use as medicinal, how the treating health care provider records the marijuana use, and lastly how the SAMHSA coder interprets the report. All of these aspects will vary greatly between states with medical marijuana laws and states without medical marijuana laws. Thus, even though estimates are reported for medical marijuana related ED visits, medical marijuana estimates cannot be assessed with any acceptable accuracy at this time, as FDA has not approved marijuana treatment of any medical condition. These data show the difficulty in evaluating abuse of a product that is not currently approved by FDA, but authorized for medical use, albeit inconsistently, at the state level. Thus, we believe the likelihood of the treating health care provider or SAMHSA coder attributing the ED visit to "medical marijuana" versus "marijuana" to be very low. Overall, the available data are inadequate to characterize its abuse at the community level.

Treatment Episode Data Set (TEDS)[17]

[17] The TEDS system is part of SAMHSA's Drug and Alcohol Services Information System (Office of Applied Science, SAMHSA). The TEDS report presents information on the demographic and substance use characteristics of the 1.8 million annual admissions to treatment for alcohol and drug abuse in facilities that report to individual state administrative data systems. Specifically, TEDS includes facilities licensed or certified by the states to provide substance abuse treatment and is required by the states to provide TEDS client-level data. Facilities that report TEDS data are those receiving State alcohol and drug agency funds for the provision of alcohol and drug treatment services. Since TEDS is based only on reports from these facilities, TEDS data do not represent the total national demand for substance abuse treatment or the prevalence of substance abuse in the general population. The primary

Primary marijuana abuse accounted for 18.1 percent of all 2011 TEDS[18] admissions. Individuals admitted for primary marijuana abuse were nearly three-quarters (73.4 percent) male, and almost half (45.2 percent) were white. The average age at admission was 24 years old, and 31.1 percent of individuals admitted for primary marijuana abuse were under the age of 18. The reported frequency of marijuana use was 24.3 percent reporting daily use. Almost all (96.8 percent) primary marijuana users utilized the substance by smoking. Additionally, 92.9 percent reported using marijuana for the first time before the age of 18.

An important aspect of TEDS admission data for marijuana is of the referral source for treatment. Specifically, primary marijuana admissions were less likely than all other admissions to either be self-referred or referred by an individual for treatment. Instead, the criminal justice system referred more than half (51.6 percent) of primary marijuana admissions.

Since 2003, the percent of admissions for primary marijuana abuse increased from 15.5 percent of all admissions in 2003 to 18.1 percent in 2011. This increase is less than the increase seen for admissions for primary opioids other than heroin, which increased from 2.8 percent in 2003 to 7.3 percent in 2011. In contrast, the admissions for primary cocaine abuse declined from 9.8 percent in 2003 to 2.0 percent in 2011.

5. THE SCOPE, DURATION, AND SIGNIFICANCE OF ABUSE

Under the fifth factor, the Secretary must consider the scope, duration, and significance of marijuana abuse. According to 2012 data from NSDUH and 2013 data from MTF, marijuana remains the most extensively used illegal drug in the United States, with 42.8 percent of U.S. individuals over age 12 (111.2 million) and 45.5 percent of 12th graders having used marijuana at least once in their lifetime. Although the majority of individuals over age 12 (83.1 percent) who have ever used marijuana in their lifetime do not use the drug monthly, 18.9 million individuals (7.3 percent of the U.S. population) report that they used marijuana within the past 30 days. An examination of use among various age cohorts through NSDUH demonstrates that monthly use occurs primarily among college-aged individuals, with use dropping off sharply after age 25. Additionally, NSDUH data show the number of individuals reporting past-month use of marijuana has increased by 4.3 million individuals since 2004. Data from MTF shows that annual prevalence of marijuana use declined for all three grades from 2005 through 2007, then began to rise through 2013. Additionally, in 2013, 1.1 percent of 8th graders, 4.0 percent of 10th graders, and 6.5 percent of 12th graders reported daily use of marijuana, defined as use on 20 or more days within the past 30 days.

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goal for TEDS is to monitor the characteristics of treatment episodes for substance abusers. Importantly, TEDS is an admissions-based system, where admittance to treatment is counted as an anonymous tally. For instance, a given individual who is admitted to treatment twice within a given year would be counted as two admissions. The most recent year with complete data is 2011.

[18] 2011; http://www.samhsa.gov/data/DASIS.aspx?qr=t#TEDS

The 2011 DAWN data show that marijuana use was mentioned in 455,668 ED visits, which amounts to approximately 36.4 percent of all illicit drug-related ED visits.[19]

TEDS data for 2011 show that 18.1 percent of all admissions were for primary marijuana abuse.[20] Between 2003 and 2011, there was a 2.6 percent increase in the number of TEDS admissions for primary marijuana use. Approximately 61.5 percent of primary marijuana admissions in 2011 were for individuals under the age of 25 years.

6. What, If Any, Risk There is to The Public Health

Under the sixth factor, the Secretary must consider the risks posed to the public health by marijuana. Factors 1, 4, and 5 include a discussion of the risk to the public health as measured by emergency room episodes and drug treatment admissions. Additionally, Factor 2 includes a discussion of marijuana's central nervous system, cognitive, cardiovascular, autonomic, respiratory, and immune system effects. Factor 6 focuses on the health risks to the individual user in terms of the risks from acute and chronic use of marijuana, as well as the "gateway hypothesis."

Risks from Acute Use of Marijuana

Acute use of marijuana impairs psychomotor performance, including complex task performance, which makes operating motor vehicles or heavy equipment after using marijuana inadvisable (Ramaekers et al., 2004; Ramaekers et al., 2006a). A meta-analysis conducted by Li et al. (2011) showed an association between marijuana use by the driver and a significantly increased risk of involvement in a car accident. Additionally, in a minority of individuals who use marijuana, some potential responses include dysphoria and psychological distress, including prolonged anxiety reactions (Haney et al., 1999).

Risks from Chronic Use of Marijuana

A distinctive marijuana withdrawal syndrome following long term or chronic use has been identified. The withdrawal syndrome indicates that marijuana produces physical dependence that is mild, short-lived, and comparable to tobacco withdrawal (Budney et al., 2008). Marijuana withdrawal syndrome is described in detail below under Factor 7.

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[19] Many factors can influence the estimates of ED visits, including trends in the reasons for ED usage. For instance, some drug users may visit EDs for life-threatening issues while others may visit to seek care for detoxification because they needed certification before entering treatment. Additionally, DAWN data do not distinguish the drug responsible for the ED visit from other drugs that may have been used concomitantly. As stated in a DAWN report, "Since marijuana/hashish is frequently present in combination with other drugs, the reason for the ED visit may be more relevant to the other drug(s) involved in the episode."

[20] An important aspect of TEDS admission data for marijuana is of the referral source for treatment. Specifically, primary marijuana admissions were less likely than all other admissions to either be self-referred or referred by an individual for treatment. Instead, the criminal justice system referred more than half (51.6 percent) of primary marijuana admissions.

The following states how the DSM-V (2013) of the American Psychiatric Association describes the consequences of *Cannabis*[21] abuse:

> Individuals with cannabis use disorder may use cannabis throughout the day over a period of months or years, and thus may spend many hours a day under the influence. Others may use less frequently, but their use causes recurrent problems related to family, school, work, or other important activities (e.g., repeated absences at work; neglect of family obligations). Periodic cannabis use and intoxication can negatively affect behavioral and cognitive functioning and thus interfere with optimal performance at work or school, or place the individual at increased physical risk when performing activities that could be physically hazardous (e.g., driving a car; playing certain sports; performing manual work activities, including operating machinery). Arguments with spouses or parents over the use of cannabis in the home, or its use in the presence of children, can adversely impact family functioning and are common features of those with cannabis use disorder. Last, individuals with cannabis use disorder may continue using marijuana despite knowledge of physical problems (e.g., chronic cough related to smoking) or psychological problems (e.g., excessive sedation or exacerbation of other mental health problems) associated with its use.

Marijuana as a "Gateway Drug"

Kandel (1975) proposed nearly 40 years ago the hypothesis that marijuana is a "gateway drug" that leads to the use or abuse of other illicit drugs. Since that time, epidemiological research explored this premise. Overall, research does not support a direct causal relationship between regular marijuana use and other illicit drug use.

The studies examining the gateway hypothesis are limited. First, in general, studies recruit individuals influenced by a myriad of social, biological, and economic factors that contribute to extensive drug abuse (Hall & Lynskey, 2005). Second, most studies that test the hypothesis that marijuana use causes abuse of illicit drugs use the determinative measure *any use of an illicit drug*, rather than DSM-5 criteria for drug abuse or dependence on an illicit drug (DSM-5, 2013). Consequently, although an individual who used marijuana may try other illicit drugs, the individual may not regularly use drugs, or have a diagnosis of drug abuse or dependence.

Little evidence supports the hypothesis that initiation of marijuana use leads to an abuse disorder with other illicit substances. For example, one longitudinal study of 708 adolescents demonstrated that early onset marijuana use did not lead to problematic drug use (Kandel & Chen, 2000). Similarly, Nace et al. (1975) examined Vietnam-era soldiers who extensively abused marijuana and heroin while they were in the military, and found a lack of correlation of a causal relationship demonstrating marijuana use leading to heroin addiction. Additionally, in another longitudinal study

[21] *Cannabis* is the term used in the DSM-V to refer to marijuana. In the following excerpt the term *Cannabis* is interchangeable for the term *marijuana*.

of 2,446 adolescents, marijuana dependence was uncommon but when it did occur, the common predictors of marijuana dependence were the following: parental death, deprived socio-economic status, and baseline illicit drug use other than marijuana (von Sydow et al., 2002).

When examining the association between marijuana and illicit drugs, focusing on drug use versus abuse or dependence, different patterns emerge. For example, a study examining the possible causal relationship of the gateway hypothesis found a correlation between marijuana use in adolescents and other illicit drug use in early adulthood and, adjusting for age-linked experiences, did not effect this correlation (Van Gundy and Rebellon, 2010). However, when examining the association in terms of development of drug abuse, age-linked stressors and social roles moderated the correlation between marijuana use in adolescents and other illicit drug abuse. Similarly, Degenhardt et al. (2009) examined the development of drug dependence and found an association that did not support the gateway hypothesis. Specifically, drug dependence was significantly associated with the use of other illicit drugs prior to marijuana use.

Interestingly, the order of initiation of drug use seems to depend on the prevalence of use of each drug, which varies by country. Based on the World Health Organization (WHO) World Mental Health Survey that includes data from 17 different countries, the order of drug use initiation varies by country and relates to prevalence of drug use in each country (Degenhardt et al., 2010). Specifically, in the countries with the lowest prevalence of marijuana use, use of other illicit drugs before marijuana was common. This sequence of initiation is less common in countries with higher prevalence of marijuana use. A study of 9,282 households in the United States found that marijuana use often preceded the use of other illicit drugs; however, prior non-marijuana drug dependence was also frequently correlated with higher levels of illicit drug abuse (Degenhardt et al., 2009). Additionally, in a large 25-year longitudinal study of 1,256 New Zealand children, the author concluded that marijuana use correlated to an increased risk of abuse of other drugs, including cocaine and heroin (Fergusson et al., 2005).

Although many individuals with a drug abuse disorder may have used marijuana as one of their first illicit drugs, this fact does not correctly lead to the reverse inference that most individuals who used marijuana will inherently go on to try or become regular users of other illicit drugs. Specifically, data from the 2011 NSDUH survey illustrates this issue (SAMHSA, 2012). NSDUH data estimates 107.8 million individuals have a lifetime history of marijuana use, which indicates use on at least one occasion, compared to approximately 36 million individuals having a lifetime history of cocaine use and approximately 4 million individuals having a lifetime history of heroin use. NSDUH data do not provide information about each individual's specific drug history. However, even if one posits that every cocaine and heroin user previously used marijuana, the NSDUH data show that marijuana use at least once in a lifetime does not predict that an individual will also use another illicit drug at least once.

Finally, a review of the gateway hypothesis by Vanyukov et al. (2012) notes that because the gateway hypothesis only addresses the order of drug use initiation, the gateway hypothesis does not specify any mechanistic connections between drug "stages" following exposure to marijuana and does not extend to the risks for addiction. This concept contrasts with the concept of a common liability to addiction that involves mechanisms and biobehavioral characteristics pertaining to the entire course of drug abuse risk and disorders.

7. ITS PSYCHIC OR PHYSIOLOGIC DEPENDENCE LIABILITY

Under the seventh factor, the Secretary must consider marijuana's psychic or physiological dependence liability.

Psychic or psychological dependence has been shown in response to marijuana's psychoactive effects. Psychoactive responses to marijuana are pleasurable to many humans and are associated with drug-seeking and drug-taking (Maldonado, 2002). Moreover, high levels of psychoactive effects, notably positive reinforcement, are associated with increased marijuana use, abuse, and dependence (Scherrer et al., 2009; Zeiger et al., 2010). Epidemiological data support these findings through 2012 NSDUH statistics that show that of individuals years 12 or older who used marijuana in the past month, an estimated 40.3 percent used marijuana on 20 or more days within the past month. This equates to approximately 7.6 million individuals aged 12 or older who used marijuana on a daily or almost daily basis. Additionally, the 2013 MTF data report the prevalence of daily marijuana use, defined as use on 20 or more days within the past 30 days, in 8^{th}, 10^{th}, and 12^{th} graders is 1.1 percent, 4.0 percent, and 6.5 percent, respectively.

Tolerance is a state of adaptation where 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 some, but not all, of marijuana's effects. Specifically, tolerance does not seem to develop in response to many of marijuana's psychoactive effects. This lack of tolerance may relate to electrophysiological data demonstrating that chronic delta^9-THC administration does not affect increased neuronal firing in the ventral tegmental area, a region known to play a critical role in drug reinforcement and reward (Wu and French, 2000). In the absence of other abuse indicators, such as rewarding properties, the presence of tolerance or physical dependence does not determine whether a drug has abuse potential.

However, humans can develop tolerance to marijuana's cardiovascular, autonomic, and behavioral effects (Jones et al., 1981). Tolerance to some of marijuana's behavioral effects seems to develop after heavy marijuana use, but not after occasional marijuana use. For instance, following acute administration of marijuana, heavy marijuana users did not exhibit impairments in tracking and attention tasks, as were seen in occasional marijuana users (Ramaekers et al., 2009). Furthermore, a neurophysiological assessment administered

through an electroencephalograph (EEG) which measures event-related potentials (ERP) conducted in the same subjects as the previous study, found a corresponding effect in the P100[22] component of ERPs. Specifically, corresponding to performance on tracking and attention tasks, heavy marijuana users showed no changes in P100 amplitudes following acute marijuana administration, although occasional users showed a decrease in P100 amplitudes (Theunissen et al., 2012). A possible mechanism underlying tolerance to marijuana's effects may be the down-regulation of cannabinoid receptors (Hirvonen et al., 2012; Gonzalez et al., 2005; Rodriguez de Fonseca et al., 1994; Oviedo et al., 1993).

Importantly, pharmacological tolerance alone does not indicate a drug's physical dependence liability. In order for physical dependence to exist, evidence of a withdrawal syndrome is needed. 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*). Many medications not associated with abuse or addiction can produce physical dependence and withdrawal symptoms after chronic use.

Discontinuation of heavy, chronic marijuana use has been shown to lead to physical dependence and withdrawal symptoms (American Psychiatric Association DSM-V, 2013; Budney and Hughes, 2006; Haney et al., 1999). In heavy, chronic marijuana users, the most commonly reported withdrawal symptoms are sleep difficulties, decreased appetite or weight loss, irritability, anger, anxiety or nervousness, and restlessness. Some less commonly reported withdrawal symptoms are depressed mood, sweating, shakiness, physical discomfort, and chills (Budney and Hughes, 2006; Haney et al., 1999). The occurrence of marijuana withdrawal symptoms in light or non-daily marijuana users has not been established. The American Psychiatric Association's DSM-V (2013) includes a list of symptoms of "cannabis withdrawal." Most marijuana withdrawal symptoms begin within 24-48 hours of discontinuation, peak within 4-6 days, and last for 1-3 weeks. Marijuana withdrawal syndrome has been reported in adolescents and adults admitted for substance abuse treatment.

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. Multiple studies comparing marijuana and tobacco withdrawal symptoms in humans demonstrate that the magnitude and time course of the two withdrawal syndromes are similar (Budney et al., 2008; Vandrey et al., 2005, 2008).

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

Under the eight factor analysis, the Secretary must consider whether marijuana is an immediate precursor of a controlled substance. Marijuana is not an immediate precursor of another controlled substance.

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[22] The P100 component of ERPs are thought to relate to the visual processing of stimuli and can be modulated by attention.

RECOMMENDATION

After consideration of the eight factors discussed above, FDA recommends that marijuana remain in Schedule I of the CSA. NIDA concurs with this scheduling recommendation. 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:

A number of factors indicate marijuana's high abuse potential, including the large number of individuals regularly using marijuana, marijuana's widespread use, and the vast amount of marijuana available for illicit use. Approximately 18.9 million individuals in the United States (7.3 percent of the U.S. population) used marijuana monthly in 2012. Additionally, approximately 4.3 million individuals met diagnostic criteria for marijuana dependence or abuse in the year prior to the 2012 NSDUH survey. A 2013 survey indicates that by 12th grade, 36.4 percent of students report using marijuana within the past year, and 22.7 percent report using marijuana monthly. In 2011, 455,668 ED visits were marijuana-related, representing 36.4 percent of all illicit drug-related episodes. Primary marijuana use accounted for 18.1 percent of admissions to drug treatment programs in 2011. Additionally, marijuana has dose-dependent reinforcing effects, as demonstrated by data showing that humans prefer relatively higher doses to lower doses. Furthermore, marijuana use can result in psychological dependence.

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

FDA has not approved a marketing application for a marijuana drug product for any indication. The opportunity for scientists to conduct clinical research with marijuana exists, and there are active INDs for marijuana; however, marijuana does not have a currently accepted medical use for treatment in the United States, nor does marijuana 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.

[57 FR 10499, March 26, 1992]

Marijuana does not meet any of the elements for having a "currently accepted medical use." First, FDA broadly evaluated marijuana, and did not focus its evaluation on particular strains of marijuana or components or derivatives of marijuana. Since different strains may have different chemical constituents, marijuana, as identified in this petition, does not have a

known and reproducible chemistry, which would be needed to provide standardized doses. Second, there are not adequate safety studies on marijuana in the medical literature in relation to a specific, recognized disorder. Third, there are no published adequate and well-controlled studies proving efficacy of marijuana. Fourth, there is no evidence that qualified experts accept marijuana for use in treating a specific, recognized disorder. Lastly, the scientific evidence regarding marijuana's chemistry in terms of a specific *Cannabis* strain that could produce standardized and reproducible doses is not currently available, so the scientific evidence on marijuana is not widely available.

Alternately, a Schedule II drug can be considered to have a "currently accepted medical use with severe restrictions" (21 U.S.C. 812(b)(2)(B)). Yet as stated above, the lack of accepted medical use for a specific, recognized disorder precludes the use of marijuana even under conditions where its use is severely restricted.

In conclusion, to date, research on marijuana's medical use has not developed to the point where marijuana is 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:**

There are currently no FDA-approved marijuana drug products. Marijuana does not have a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions. Thus, FDA has not determined that marijuana is safe for use under medical supervision.

In addition, FDA cannot conclude that marijuana has an acceptable level of safety relative to its effectiveness in treating a specific, recognized disorder without evidence that the substance is contamination free, and assurance of a consistent and predictable dose. Investigations into the medical use of marijuana should include information and data regarding the chemistry, manufacturing, and specifications of marijuana. Additionally, a procedure for delivering a consistent dose of marijuana should also be developed. Therefore, FDA concludes marijuana does not currently have an accepted level of safety for use under medical supervision.

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ENCLOSURE 2

The Medical Application of Marijuana: A Review of Published Clinical Studies

March 19, 2015

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Executive Summary

Marijuana is a Schedule I substance under the Controlled Substances Act. Schedule I indicates a high potential for abuse, no currently accepted medical use in the United States, and a lack of accepted safety for use under medical supervision. To date, marijuana has not been subject to an approved new drug application that demonstrates its safety and efficacy for a specific indication under the Federal Food, Drug, and Cosmetic Act.

Nevertheless, as of October 2014, twenty-three states and the District of Columbia have passed state-level medical marijuana laws that allow for marijuana use within that state; similar bills are pending in other states.

The present review was undertaken by the Food and Drug Administration (FDA) to analyze the clinical studies published in the medical literature investigating the use of marijuana in any therapeutic areas. First, we discuss the context for this scientific review. Next, we describe the methods used in this review to identify adequate and well-controlled studies evaluating the safety and efficacy of marijuana for particular therapeutic uses.

The FDA conducted a systematic search for published studies in the medical literature that meet the described criteria for study design and outcome measures prior to February 2013. While not part of our systematic review, we have routinely continued to follow the literature beyond that date for subsequent studies. Studies were considered to be relevant to this review if the investigators administered marijuana to patients with a diagnosed medical condition in a well-controlled, double-blind, placebo-controlled clinical trial. Of the eleven studies that met the criteria for review, five different therapeutic areas were investigated:

- Five studies examined chronic neuropathic pain.
- Two studies examined appetite stimulation in human immunodeficiency virus (HIV) patients.
- Two studies examined glaucoma.
- One study examined spasticity and pain in multiple sclerosis (MS).
- One study examined asthma.

For each of these eleven clinical studies, information is provided regarding the subjects studied, the drug conditions tested (including dose and method of administration), other drugs used by subjects during the study, the physiological and subjective measures collected, the outcome of these measures comparing treatment with marijuana to placebo, and the reported and observed adverse events. The conclusions drawn by the investigators are then described, along with potential limitations of these conclusions based on the study design. A brief

summary of each study's findings and limitations is provided at the end of the section.

The eleven clinical studies that met the criteria and were evaluated in this review showed positive signals that marijuana may produce a desirable therapeutic outcome, under the specific experimental conditions tested. Notably, it is beyond the scope of this review to determine whether these data demonstrate that marijuana has a currently accepted medical use in the United States. However, this review concludes that these eleven clinical studies serve as proof-of-concept studies, based on the limitations of their study designs, as described in the study summaries. Proof-of-concept studies provide preliminary evidence on a proposed hypothesis regarding a drug's effect. For drugs under development, the effect often relates to a short-term clinical outcome being investigated. Proof-of-concept studies serve as the link between preclinical studies and dose ranging clinical studies. Therefore, proof-of-concept studies are not sufficient to demonstrate efficacy of a drug because they provide only preliminary information about the effects of a drug. However, the studies reviewed produced positive results, suggesting marijuana should be further evaluated as an adjunct treatment for neuropathic pain, appetite stimulation in HIV patients, and spasticity in MS patients.

The main limitations identified in the eleven studies testing the medical applications of marijuana are listed below:

- The small numbers of subjects enrolled in the studies, which limits the statistical analyses of safety and efficacy.
- The evaluation of marijuana only after acute administration in the studies, which limits the ability to determine efficacy following chronic administration.
- The administration of marijuana typically through smoking, which exposes ill patients to combusted material and introduces problems with determining the doses delivered.
- The potential for subjects to identify whether they received marijuana or placebo, which breaks the blind of the studies.
- The small number of cannabinoid-naïve subjects, which limits the ability to determine safety and tolerability in these subjects.
- The low number of female subjects, which makes it difficult to generalize the study findings to subjects of both genders.

Thus, this review discusses the following methodological changes that may be made in order to resolve these limitations and improve the design of future studies which examine the safety and efficacy of marijuana for specific therapeutic indications:

- Determine the appropriate number of subjects studied based on recommendations in various FDA guidances for industry regarding the conduct of clinical trials for specific medical indications.
- Administer consistent and reproducible doses of marijuana based on recommendations in FDA's 2004 guidance for industry entitled *Botanical Drug Products.*[1]
- Evaluate the effects of marijuana under therapeutic conditions following both acute and chronic administration.
- Consider alternatives to smoked marijuana (e.g., vaporization).
- Address and improve, whenever possible, the difficulty in blinding of marijuana and placebo treatments in clinical studies.
- Evaluate the effect of prior experience with marijuana with regard to the safety and tolerability of marijuana.
- Strive for gender balance in the subjects used in studies.

In conclusion, the eleven clinical studies conducted to date do not meet the criteria required by the FDA to determine if marijuana is safe and effective in specific therapeutic areas. However, the studies can serve as proof-of-concept studies and support further research into the use of marijuana in these therapeutic indications. Additionally, the clinical outcome data and adverse event profiles reported in these published studies can beneficially inform how future research in this area is conducted. Finally, application of the recommendations listed above by investigators when designing future studies could greatly improve the available clinical data that can be used to determine if marijuana has validated and reliable medical applications.

[1] This guidance is available on the internet at http://www.fda.gov/Drugs/default.htm under Guidance (Drugs).

1. Introduction

In response to citizen petitions submitted to the Drug Enforcement Administration (DEA) requesting DEA to reschedule marijuana, the DEA Administrator requested that the U.S. 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 21 U.S.C. 811(b). The Secretary of HHS is required to consider in a scientific and medical evaluation eight factors determinative of control under the Controlled Substance Act (CSA). 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). Part of this evaluation includes an assessment of whether marijuana has a currently accepted medical use in the United States. This assessment necessitated a review of the available data from published clinical studies to determine whether there is adequate scientific evidence of marijuana's effectiveness.

Under Section 202 of the CSA, marijuana is currently controlled as a Schedule I substance (21 U.S.C § 812). Schedule I includes those substances that have a high potential for abuse, have no currently accepted medical use in treatment in the United States, and lack accepted safety for use under medical supervision (21 U.S.C. § 812(b)(1)(A)-(C)).

A drug product which has been approved by FDA for marketing in the United States is considered to have a "currently accepted medical use." Marijuana is not an FDA-approved drug product, as a New Drug Application (NDA) or Biologics License application (BLA) for marijuana has not been approved by FDA. However, FDA approval of an NDA is not the only means through which a drug can have a currently accepted medical use in the United States.

In general, a drug may have a "currently accepted medical use" in the United States if the drug meets a five-part test. Established case law (Alliance for Cannabis Therapeutics v. DEA, 15 F.3d 1131, 1135 (D.C. Cir. 1994)) upheld the Administrator of DEA's application of the five-part test to determine whether a drug has a "currently accepted medical use." The following describes the five elements that characterize "currently accepted medical use" for a drug[2]:

i. the drug's chemistry must be known and reproducible

> "The substance's chemistry must be scientifically established to permit it to be reproduced into dosages which can be standardized. The listing of the substance in a current edition of one of the official compendia, as defined by section 201(j)

[2] 57 FR 10499, 10504-06 (March 26, 1992).

> of the Food, Drug and Cosmetic Act, 21 U.S.C. 321(j), is sufficient to meet this requirement."

ii. there must be adequate safety studies

> "There must be adequate pharmacological and toxicological studies, done by all methods reasonably applicable, on the basis of which it could fairly and responsibly be concluded, by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, that the substance is safe for treating a specific, recognized disorder."

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

> "There must be adequate, well-controlled, well-designed, well-conducted, and well-documented studies, including clinical investigations, by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, on the basis of which it could be fairly and responsibly concluded by such experts that the substance will have the intended effect in treating a specific, recognized disorder."

iv. the drug must be accepted by qualified experts

> "The drug has a New Drug Application (NDA) approved by the Food and Drug Administration, pursuant to the Food, Drug and Cosmetic Act, 21 U.S.C. 355. Or, a consensus of the national community of experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, accepts the safety and effectiveness of the substance for use in treating a specific, recognized disorder. A material conflict of opinion among experts precludes a finding of consensus." and

v. the scientific evidence must be widely available.

> "In the absence of NDA approval, information concerning the chemistry, pharmacology, toxicology, and effectiveness of the substance must be reported, published, or otherwise widely available, in sufficient detail to permit experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, to fairly and responsibly conclude the substance is safe and effective for use in treating a specific, recognized disorder."

One way to pass the five-part test for having a "currently accepted medical use" is through submission of an NDA or BLA which is approved by FDA. However,

FDA approval of an NDA or BLA is not required for a drug to pass the five-part test.

This review focuses on FDA's analysis of one element of the five-part test for determining whether a drug has a "currently accepted medical use." Specifically, the present review assesses the 3rd criterion that addresses whether marijuana has "adequate and well-controlled studies proving efficacy." Thus, this review evaluates published clinical studies that have been conducted using marijuana in subjects who have a variety of medical conditions by assessing the adequacy of the summarized study designs and the study data. The methodology for selecting the studies that were evaluated is delineated below.

FDA's evaluation and conclusions regarding the remaining four criteria for whether marijuana has a "currently accepted medical use," as well as the eight factors pertaining to the scheduling of marijuana, are outside the scope of this review. A detailed discussion of these factors is contained in FDA's scientific and medical evaluation of marijuana.

2. Methods

The methods for selecting the studies to include in this review involved the following steps, which are described in detail in the subsections below:

1. Define the objective of the review,
2. Define "marijuana" in order to facilitate the medical literature search for studies that administered the substance,
3. Define "adequate and well-controlled studies" in order to facilitate the search for relevant data and literature,
4. Search medical literature databases and identify relevant adequate and well-controlled studies, and
5. Review and analyze the adequate and well-controlled clinical studies to determine if they demonstrate efficacy of marijuana for any therapeutic indication.

2.1 Define the Objective of the Review

The objective of this review is to assess the study designs and resulting data from clinical studies published in the medical literature that were conducted with marijuana (as defined below) as a treatment for any therapeutic indication, in order to determine if they meet the criteria of "adequate and well-controlled studies proving efficacy."

2.2 Define "Marijuana"

In this review, the term "marijuana" refers to the flowering tops or leaves of the *Cannabis* plant. There were no restrictions on the route of administration used for marijuana in the studies.

Studies which administered individual cannabinoids (whether experimental substances or marketed drug products) or marijuana extracts were excluded from this review. Additionally, studies of administered neutral plant material or placebo marijuana (marijuana with all cannabinoids extracted) that had subsequently been supplemented by the addition of specific amounts of tetrahydrocannabinol (THC) or other cannabinoids were also excluded (Chang et al., 1979).

2.3 Define "Adequate and Well-Controlled Clinical Studies"

The criteria for an "adequate and well-controlled study" for purposes of determining the safety and efficacy of a human drug is defined under the Code of Federal Regulations (CFR) in 21 CFR 314.126. The elements of an adequate and well-controlled study as described in 21 CFR 314.126 can be summarized as follows:

1. The main objective must be to assess a therapeutically relevant outcome.
2. The study must be placebo-controlled.
3. The subjects must qualify as having the medical condition being studied.
4. The study design permits a valid comparison with an appropriate control condition.
5. The assignment of subjects to treatment and control groups must be randomized.
6. There is minimization of bias through the use of a double-blind study design.
7. The study report contains a full protocol and primary data.
8. Analysis of the study data is appropriately conducted.

As noted above, the current review examines only those data available in the public domain and thus relies on clinical studies published in the medical literature. Published studies by their nature are summaries that do not include the level of detail required by studies submitted to FDA in an NDA.

While the majority of the elements defining an adequate and well-controlled study can be satisfied through a published paper (elements #1-6), there are two elements that cannot be met by a study published in the medical literature: element #7 (availability of a study report with full protocol and primary data) and element #8 (a determination of whether the data analysis was appropriate). Thus, for purposes of this review, only elements #1-6 will be used to qualify a study as being adequate and well-controlled.

2.4 Search Medical Literature Databases and Identify Relevant Studies

We identified randomized, double-blind, placebo-controlled clinical studies conducted with marijuana to assess marijuana's efficacy in any therapeutic indication. Two primary medical literature databases were searched for all studies posted to the databases prior to February 2013[3]:

- PubMed: PubMed is a database of published medical and scientific studies that is maintained by the U.S. National Library of Medicine (NLM) at the National Institute of Health (NIH) as a part of the Entrez system of information retrieval. PubMed comprises more than 24 million citations for biomedical literature from MEDLINE, life science journals, and online books (http://www.ncbi.nlm.nih.gov/pubmed).

- ClinicalTrials.gov: ClinicalTrials.gov is a database of publicly and privately supported clinical studies that is maintained by the NLM. Information about the clinical studies is provided by the sponsor or Principal Investigator of the study. Information about the studies is submitted to the website ("registered") when the studies begin, and is updated throughout the study. In some cases, results of the study or resulting publication citations are submitted to the website after the study ends (https://clinicaltrials.gov/ct2/about-site/background).

ClinicalTrials.gov was searched for all studies administering marijuana. The results of this search were used to confirm that no completed studies with published data were missed in the literature search. During the literature search, references found in relevant studies and systematic reviews were evaluated for additional relevant citations. All languages were included in the search. The PubMed search yielded a total of 566 abstracts.[4] Of these abstracts, a full-text review was conducted with 85 papers to assess eligibility. From this evaluation, only 11 of 85 studies met the 6 CFR elements for inclusion as adequate and well-controlled studies.

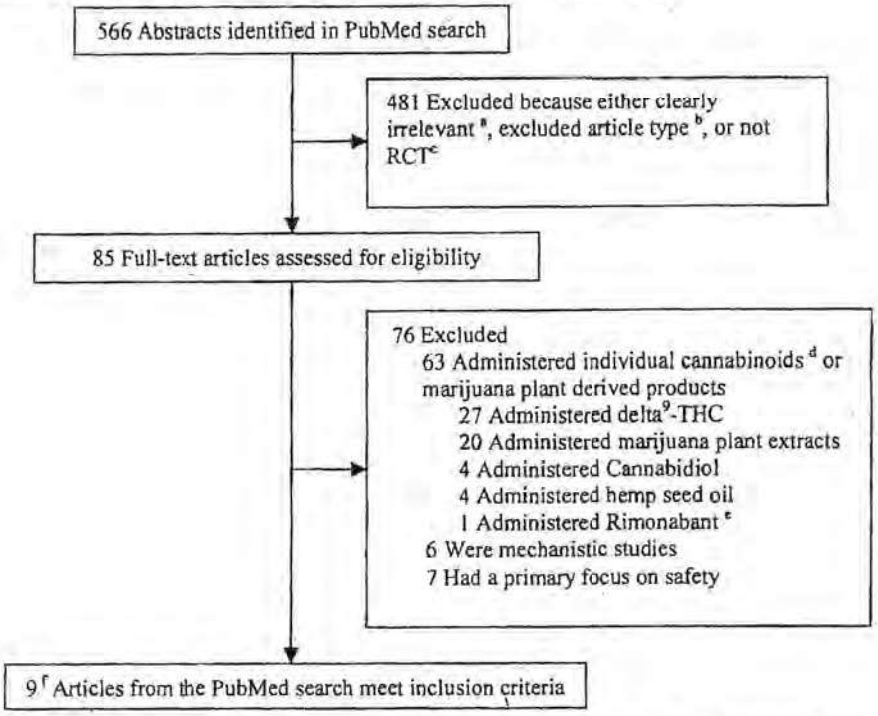
Figure 1 (below) provides an overview of the process used to identify studies from the PubMed search. The eleven studies reviewed were published between 1974 and 2013. Ten of these studies were conducted in the United States and one study was conducted in Canada. These eleven studies examined the effects of smoked and vaporized marijuana for the indications of chronic neuropathic pain, spasticity related to multiple sclerosis (MS), appetite stimulation in patients with human immunodeficiency virus (HIV), glaucoma, and asthma. All included studies used adult patients as subjects. All studies conducted in the United States

[3] While not a systematic review, we have followed the recent published literature on marijuana use for possible therapeutic purposes and, as of January 2015, we found only one new study that would meet our criteria (Naftali et al., 2013). This study examined the effects of smoked marijuana on Crohn's disease.

[4] The following search strategy was used, "(cannabis OR marijuana) AND (therapeutic use OR therapy) AND (RCT OR randomized controlled trial OR "systematic review" OR clinical trial OR clinical trials) NOT ("marijuana abuse"[Mesh] OR addictive behavior OR substance related disorders)".

were conducted under an investigational new drug (IND) as Phase 2 investigations.

Figure 1: Identification of Studies from PubMed Search



[a]Articles were deemed irrelevant if they examined safety or adverse event related outcomes, including psychoactive effects or other adverse events. [b]Excluded article types included comments, reviews, meta-analyses, and news articles. [c]Randomized Controlled Trials. [d]Cannabinoids administered included synthetic cannabinoids. [e]Rimonabant is a cannabinoid receptor antagonist. [f]An additional 2 studies meeting the inclusion criteria were found through the reference search.

Two qualifying studies, which assessed marijuana for glaucoma, were previously reviewed in the 1999 Institute of Medicine (IOM) report entitled "Marijuana and Medicine: Assessing the Science Base."[5] We did our own analysis of these two studies and concurred with the conclusions in the IOM report. Thus, a detailed discussion of the two glaucoma studies is not included in the present review. The present review only discusses 9 of the identified 11 studies. For a summary of the study design for all 11 qualifying studies, see Tables 1-5 (located in the Appendix).

[5] In January 1997, the White House Office of National Drug Control Policy (ONDCP) requested that the IOM conduct a review of the scientific evidence to assess the potential health benefits and risks of marijuana and its constituent cannabinoids. Information for this study was gathered through scientific workshops, site visits to cannabis buyers' clubs and HIV/Acquired Immunodeficiency Syndrome (AIDS) clinics, analysis of the relevant scientific literature, and extensive consultation with biomedical and social scientists. The report was finalized and published in 1999.

Based on the selection criteria for relevant studies described in Section 2.3 ("Define 'Adequate and Well-Controlled Clinical Studies'"), a number of clinical studies that investigated marijuana, as defined in this review, were excluded from this review. Studies that examined the effects of marijuana in healthy subjects were excluded because they did not test a patient population with a medical condition (Flom et al., 1975; Foltin et al., 1986; Foltin et al., 1988; Hill et al., 1974; Milstein et al., 1974; Milstein et al., 1975; Soderpalm et al., 2001; Wallace et al., 2007; Greenwald and Stitzer, 2000). A 1975 study by Tashkin et al. was excluded because it had a single-blind, rather than double-blind, study design. Two other studies were excluded because the primary outcome measure assessed safety rather than a therapeutic outcome (Greenberg et al., 1994; Abrams et al., 2003).

2.5 Review and Analyze Qualifying Clinical Studies

Qualified clinical studies that evaluated marijuana for therapeutic purposes were examined in terms of adequacy of study design including method of drug administration, study size, and subject inclusion and exclusion criteria. Additionally, the measures and methods of analysis used in the studies to assess the treatment effect were examined.

3. Results and Discussion

The 11 qualifying studies in this review assessed a variety of therapeutic indications. In order to better facilitate analysis and discussion of the studies, the following sections group the studies by therapeutic area. Within each section, each individual study is summarized in terms of its design, outcome data, and important limitations. This information is also provided in the Appendix in tabular form for each study.

3.1 Neuropathic Pain

Five randomized, double-blind, placebo-controlled Phase 2 clinical studies have been conducted to examine the effects of inhaled marijuana smoke on neuropathic pain associated with HIV-sensory neuropathy (Abrams et al., 2007; Ellis et al., 2009) and chronic neuropathic pain from multiple causes (Wilsey et al., 2008; Ware et al., 2010; Wilsey et al., 2013). Table 1 of the Appendix summarizes these studies.

3.1.1 Neuropathic Pain Associated with HIV-Sensory Neuropathy

Two studies examined the effect of marijuana to reduce the pain induced by HIV-sensory neuropathy.

Abrams et al. (2007) conducted the first study entitled "Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial." The

subjects were 50 adult patients with uncontrolled HIV-associated sensory neuropathy, who had at least 6 experiences with smoking marijuana. The subjects were split into two parallel groups of 25 subjects each. More than 68% of subjects were current marijuana users, but all individuals were required to discontinue using marijuana prior to the study. Most subjects were taking medication for pain during the study, with the most common medications being opioids and gabapentin. Upon entry into the study, subjects had an average daily pain score of at least 30 on a 0-100 visual analog scale (VAS).

Subjects were randomized to receive either smoked marijuana (3.56% THC[6]) or smoked placebo cigarettes three times per day for 5 days, using a standardized cued smoking procedure: (1) 5-second inhale, (2) 10-second holding smoke in the lungs, (3) 40-second exhale and breathing normally between puffs. The authors did not specify how many puffs the subjects smoked at each smoking session, but they stated that one cigarette was smoked per smoking session.

Primary outcome measures included daily VAS ratings of chronic pain and the percentage of subjects who reported a result of more than 30% reduction in pain intensity. The ability of smoked marijuana to induce acute analgesia was assessed using both thermal heat model and capsaicin sensitization model, while anti-hyperalgesia was assessed with brush and von Frey hair stimuli. The immediate analgesic effects of smoked marijuana was assessed using a 0-100 point VAS at 40-minute intervals three times before and three times after the first and last smoking sessions, which was done to correspond to the time of peak plasma cannabinoid levels. Notably, not all subjects completed the induced pain portion of the study (n=11 in marijuana group, 9 in placebo group) because of their inability to tolerate the stimuli. Throughout the study, subjects also completed the Profile of Mood States (POMS) questionnaire, as well as subjective VAS measures of anxiety, sedation, disorientation, paranoia, confusion, dizziness, and nausea.

As a result, the median daily pain was reduced 34% by smoked marijuana compared to 17% by placebo (p=0.03). Of those subjects who smoked marijuana, 52% reported a >30% reduction in pain compared to 24% in the placebo group (p=0.04). Although marijuana reduced experimentally induced hyperalgesia ($p \leq 0.05$) during the first smoking sessions, marijuana did not alter responses to acutely painful stimuli.

There were no serious adverse events (AEs) and no episodes of hypertension, hypotension, or tachycardia requiring medical intervention. No subjects withdrew from the study for drug-related reasons. Subjects in the marijuana group reported higher ratings on the subjective measures of anxiety, sedation, disorientation, confusion, and dizziness compared to the placebo group. There was one case of

[6] The drug dose is reported as percentage of THC present in the marijuana rather than milligrams of THC present in each cigarette because of the difficulty in determining the amount of THC delivered by inhalation (see discussion in the section entitled "3.7.2 Marijuana Dose Standardization").

severe dizziness in a marijuana-treated subject. By the end of the study, subjects treated with marijuana and placebo reported a reduction in total mood disturbance as measured by POMS.

The authors conclude that smoked marijuana effectively reduced chronic neuropathic pain from HIV-associated sensory neuropathy with tolerable side effects. However, limitations of this study include: maintenance of subjects on other analgesic medication while being tested with marijuana and a lack of information about the number of puffs during each inhalation of smoke. These limitations make it difficult to conclude that marijuana has analgesic properties on its own and that the actual AEs experienced during the study in response to marijuana are tolerable. However, the study produced positive results suggesting that marijuana should be studied further as an adjunct treatment for uncontrolled HIV-associated sensory neuropathy.

Ellis et al. (2009) conducted a more recent study entitled "Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial." The subjects were 28 HIV-positive adult male patients with intractable neuropathic pain that was refractory to the effects of at least two drugs taken for analgesic purposes. Upon entry into the study, subjects had a mean score of > 5 on the Pain Intensity subscale of the Descriptor Differential Scale (DDS). Subjects were allowed to continue taking their current routine of pain medications, which included opioids, non-narcotic analgesics, antidepressants, and anticonvulsants. Previous experience with marijuana was not required for participation in the study, but 27 of 28 subjects (96%) reported previous experience with marijuana. However, of these 27 experienced subjects, 63% (n=18) reported no marijuana use within the past year.

The study procedures compared the effects of the target dose of marijuana and placebo during two treatment periods lasting 5 days, with 2-week washout periods. The marijuana strengths available were 1%, 2%, 4%, 6%, or 8% THC concentration by weight. Subjects smoked marijuana or placebo cigarettes four times per day, approximately 90-120 minutes apart, using a standardized cued smoking procedure: (1) 5-second smoke inhalation, (2) 10-second hold of smoke in lungs, (3) 40-second exhale and normal breathing between puffs. The investigators did not provide a description of the number of puffs taken at any smoking session. All subjects practiced the smoking procedures using placebo marijuana prior to test sessions.

On the first day of each test period, dose titration occurred throughout the four smoking sessions scheduled for that day, with a starting strength of 4% THC concentration. Subjects were allowed to titrate to a personalized "target dose," which was defined as the dose that provided the best pain relief without intolerable adverse effects. This dose titration was accomplished by allowing subjects to either increase the dose incrementally (to 6% or 8% THC) to improve analgesia, or to decrease the dose incrementally (to 1% or 2% THC) if AEs were intolerable. For the next 4 days of each test period, the subjects smoked their

target dose during each of the four daily smoking sessions. To maintain the blind, placebo marijuana was represented as containing 1%-8% THC, even though it did not contain any cannabinoids.

The primary outcome measure was the change in pain magnitude on the DDS at the end of each test period compared to baseline, with a clinically significant level of analgesia considered to be a reduction in pain of at least 30%. Additional measures included the POMS, the Sickness Impact Profile (SIP), the Brief Symptom Inventory (BSI), and the UKU Side Effect Rating Scale and a subjective highness/sedation VAS.

During the marijuana treatment week, 19 subjects titrated to the 2%-4% THC dose while the 6%-8% dose was preferred by 8 subjects and 1 subject chose the 1% dose. In contrast, during the placebo treatment week, all 28 subjects titrated to the highest possible dose of "8% THC" that contained no actual cannabinoids, suggesting that placebo treatment provided little analgesic relief.

The degree of pain reduction was significantly greater after administration of marijuana compared to placebo (median change of 3.3 points on DDS, p=0.016). The median change from baseline in VAS pain scores was −17 for marijuana treatment compared to −4 for placebo treatment (p<0.001). A larger proportion of subjects who were treated with marijuana (0.46) reported a >30% reduction in pain, compared to placebo (0.18). Additionally, the authors report improvements in total mood disturbance, physical disability, and quality of life as measured on POMS, SIP, and BSI scales after both placebo and marijuana treatment (data not provided in paper).

In terms of safety, there were no alterations in HIV disease parameters in response to marijuana or placebo. The authors report that marijuana led to a greater degree of UKU responses as well as AEs such as difficulty in concentration, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation and thirst compared to placebo (data not provided in paper). Two subjects withdrew from the study because of marijuana-related AEs: one subject developed an intractable smoking-related cough during marijuana administration and the sole marijuana-naïve subject in the study experienced an incident of acute cannabis-induced psychosis.[7]

The authors conclude that smoked marijuana effectively reduced chronic neuropathic pain from HIV-associated sensory neuropathy. The limitations of this study include: a lack of information about the number of puffs during each inhalation of smoke; a lack of information about the specific timing of the subjective assessments and collection of AEs relative to initiation of the smoking

[7] At the time of the study, the following criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR, 2000) were used to diagnose substance-induced psychotic disorders: prominent hallucinations or delusions; hallucinations and/or delusions that develop during, or within one month of, intoxication or withdrawal; the disturbance is not better accounted for by a psychotic disorder that is not substance induced. The disturbance does not occur exclusively during the course of a delirium.

sessions; and the inclusion of only one marijuana-naïve subject. These limitations make it difficult to conclude that the actual AEs experienced during the study in response to marijuana are tolerable. It is especially concerning that the only marijuana-naïve subject left the study because of serious psychiatric responses to marijuana exposure at analgesic doses. However, the study produced positive results suggesting that marijuana should be studied further as an adjunct treatment for uncontrolled HIV-associated sensory neuropathy.

3.1.2 Central and Peripheral Neuropathic Pain

Three studies examined the effect of marijuana on chronic neuropathic pain.

Wilsey et al. (2008) examined chronic neuropathic pain from multiple causes in the study entitled "A Randomized, Placebo-Controlled, Crossover Trial of Cannabis Cigarettes in Neuropathic Pain." The subjects were 32 patients with a variety of neuropathic pain conditions, including 22 with complex regional pain syndrome, 6 with spinal cord injury, 4 with multiple sclerosis, 3 with diabetic neuropathy, 2 with ilioinguinal neuralgia, and 1 with lumbosacral plexopathy. All subjects reported a pain intensity of at least 30 on a 0-100 VAS and were allowed to continue taking their regular medications during the study period, which included opioids, antidepressants, anticonvulsants, and non-steroidal anti-inflammatory drugs (NSAIDs). All subjects were required to have experience with marijuana but could not use any cannabinoids for 30 days before study sessions.

The study consisted of three test sessions with an interval of 3-21 days between sessions. Treatment conditions were high-strength marijuana (7% delta-9-THC), low-strength marijuana (3.5% delta-9-THC), and placebo cigarettes, administered through a standardized cued-puff procedure (1) "light the cigarette" (30 seconds), (2) "get ready" (5 seconds), (3) "inhale" (5 seconds), (4) "hold smoke in lungs" (10 seconds), (5) "exhale," and (6) wait before repeating the puff cycle (40 seconds). Participants took 2 puffs after baseline measurements, 3 puffs an hour later, and 4 puffs an hour after that, for a cumulative dose of 9 puffs per test session.

Hourly assessment periods were scheduled before and after each set of puffs and for 2 additional hours during the recovery period. Plasma cannabinoids were measured at baseline, 5 minutes after the first puff and again at 3 hours after the last puff cycle.

The primary outcome measure was spontaneous pain relief, as measured by a 0-100 point VAS for current pain. Pain unpleasantness was measured on a 0-100 point VAS, and degree of pain relief was measured on a 7-point Patient Global Impression of Change (PGIC) scale. Secondary measures included the Neuropathic Pain Scale (NPS), a 0-100 point VAS for allodynia, and changes in thermal pain threshold. Subjective measures were also evaluated with unipolar 0-

100 point VAS for any drug effect, good drug effect, bad drug effect, high, drunk, impaired, stoned, like the drug effect, sedated, confused, nauseated, desire more of the drug, anxious, down, hungry, and bipolar 0-100 point VAS for sad/happy, anxious/relaxed, jittery/calm, bad/good, paranoid/self-assured, fearful/unafraid. Neurocognitive assessments measured attention and concentration, learning and memory, and fine motor speed.

Marijuana produced a reduction in pain compared to placebo, as measured by the pain VAS, the PGIC and on pain descriptors in the NPS, including sharp ($P <$ .001), burning ($P <$ .001), aching ($P <$ .001), sensitive (P=.03), superficial ($P <$ .01) and deep pain ($P <$ .001). Notably, there were no additional benefits from the 7% THC strength of marijuana compared to the 3.5% THC strength, seemingly because of cumulative drug effects over time. There were no changes in allodynia or thermal pain responsivity following administration of either dose of marijuana.

Marijuana at both strengths produced increases on measures of any drug effect, good drug effect, high, stoned, impairment, sedation, confusion, and hunger. The 7% THC marijuana increased anxiety scores and bad drug effect (later in session) compared to placebo. Neither strength of marijuana affected the measures of mood. On neurocognitive measures, both the 3.5% THC and 7% THC marijuana produced impairment in learning and memory, while only the 7% THC marijuana impaired attention and psychomotor speed, compared to placebo. There were no adverse cardiovascular side effects and no subjects dropped out because of an adverse event related to marijuana.

The authors conclude that marijuana may be effective at ameliorating neuropathic pain at doses that induce mild cognitive effects, but that smoking is not an optimum route of administration. The limitations of this study include: inclusion of subjects with many forms of neuropathic pain and maintenance of subjects on other analgesic medication while being tested with marijuana. These limitations make it difficult to conclude that marijuana has analgesic properties on its own and that the actual AEs experienced during the study in response to marijuana are tolerable. The authors compared pain score results by the type of pain condition, with no significant differences found; however, the sample size of this study was small thus a type II error may have been present. Thus, it is difficult to determine if any particular subset of neuropathic pain conditions would benefit specifically from marijuana administration. However, the study produced positive results suggesting that marijuana should be studied further as an adjunct treatment for uncontrolled neuropathic pain.

The second study, conducted by **Ware et al. (2010)** in Canada is entitled "Smoked cannabis for chronic neuropathic pain: a randomized controlled trial." The subjects were 21 adult patients with neuropathic pain caused by trauma or surgery compounded with allodynia or hyperalgesia, and a pain intensity score greater than 4 on a 10 point VAS. All subjects maintained their current analgesic medication and they were allowed to use acetaminophen for breakthrough pain.

Eighteen subjects had previous experience with marijuana but none of them had used marijuana within a year before the study.

The study design used a four-period crossover design, testing marijuana (2.5%, 6.0% and 9.4% THC) and placebo marijuana. The 2.5% and 6.0% doses of marijuana were included to increase successful blinding. Each period was 14 days in duration, beginning with 5 days on the study drug followed by a 9-day washout period. Doses were delivered as 25 mg of marijuana that was smoked in a single inhalation using a titanium pipe. The first dose of each period was self-administered using a standardized puff procedure: (1) inhale for 5 seconds, (2) hold the smoke in their lungs for 10 seconds, and (3) exhale. Subsequent doses were self-administered in the same manner for a total of three times daily at home on an outpatient basis for the first five days of each period.

The primary measure was an 11-point pain intensity scale, averaged over the 5 day treatment period, which was administered once daily for present, worst, least and average pain intensity during the previous 24 hours. Secondary measures included an acute pain 0-100 point VAS, pain quality assessed with the McGill Pain Questionnaire, sleep assessed with the Leeds Sleep Evaluation Questionnaire, mood assessed with the POMS, quality of life assessed using the EQ-5D health outcome instrument. Subjective measures included 0-100 point VAS scales for high, relaxed, stressed and happy.

Over the first three hours after smoking marijuana, ratings of pain, high, relaxation, stress, happiness and heart rate were recorded. During the five days of each study period, participants were contacted daily to administer questionnaires on pain intensity, sleep, medication and AEs. Subjects returned on the fifth day to complete questionnaires on pain quality, mood, quality of life and assessments of potency. At the end of the study, participants completed final adverse event reports and potency assessments.

The average daily pain intensity was significantly lower on 9.4% THC marijuana (5.4) than on placebo marijuana (6.1) (p=0.023). The 9.4% THC strength also produced more drowsiness, better sleep, with less anxiety and depression, compared to placebo (all $p < 0.05$). However, there were no significant differences on POMS scores or on VAS scores for high, happy, relaxed or stressed between THC doses.

The most frequent drug-related adverse events reported in the group receiving 9.4% THC marijuana were headache, dry eyes, burning sensation, dizziness, numbness, and cough. Reports of high and euphoria occurred on only three occasions, once in each dose of THC. There were no significant changes in vital signs, heart-rate variability, or renal function. One subject withdrew from the study due to increased pain during administration of 6% THC marijuana.

The authors conclude that smoked marijuana reduces neuropathic pain, improves mood and aids in sleep, but that smoking marijuana is not a preferable route of administration. The limitations of this study include: the lack of information on timing of assessments during the outpatient portion of the study and maintenance of subjects on other analgesic medication while being tested with marijuana. These limitations make it difficult to conclude that marijuana has analgesic properties on its own and that the actual AEs experienced during the study in response to marijuana are tolerable. However, the study produced positive results suggesting that marijuana should be studied further as an adjunct treatment for uncontrolled neuropathic pain.

Wilsey et al. (2013) conducted the most recent study entitled "Low-Dose Vaporized Cannabis Significantly Improves Neuropathic Pain." This study is the only one in this review that utilized vaporization as a method of marijuana administration. The subjects were 36 patients with a neuropathic pain disorder (CRPS, thalamic pain, spinal cord injury, peripheral neuropathy, radiculopathy, or nerve injury) who were maintained on their current medications (opioids, anticonvulsants, antidepressants, and NSAIDs). Although subjects were required to have a history of marijuana use, they refrained from use of cannabinoids for 30 days before study sessions.

Subjects participated in three sessions in which they received 1.29% or 3.53% THC marijuana or placebo marijuana. The marijuana was vaporized using the Volcano vaporizer and a standardized cued-puff procedure: (1) "hold the vaporizer bag with one hand and put the vaporizer mouthpiece in their mouth" (30 seconds), (2) "get ready" (5 seconds), (3) "inhale" (5 seconds), (4) "hold vapor in lungs" (10 seconds), (5) "exhale and wait" before repeating puff cycle (40 seconds). Subjects inhaled 4 puffs at 60 minutes. At 180 minutes, the vaporizer was refilled with marijuana vapor and subjects were allowed to inhale 4 to 8 puffs using the cued procedure. Thus, cumulative dosing allowed for a range of 8 to12 puffs in total for each session, depending on the subjects desired response and tolerance. The washout time between each session ranged from 3-14 days.

The primary outcome variable was spontaneous pain relief, as assessed using a 0-100 point VAS for current pain. Secondary measures included the Patient Global Impression of Change (PGIC), the NPS, and a 0-100 point VAS for allodynia. Acute pain threshold was measured with a thermal pain model. Subjective measures included 0-100 point unipolar VAS for any drug effect, good drug effect, bad drug effect, high, drunk, impaired, stoned, drug liking, sedated, confused, nauseated, desire more drug, anxious, down and hungry. Bipolar 0-100 point VAS included sad/happy, anxious/relaxed, jittery/calm, bad/good, paranoid/self-assured, and fearful/unafraid. Neurocognitive assessments assessed attention and concentration, learning and memory, and fine motor speed.

A 30% reduction in pain was achieved in 61% of subjects who received the 3.53% THC marijuana, in 57% of subjects who received the 1.29% THC

marijuana and in 26% of subjects who received the placebo marijuana ($p=0.002$ for placebo vs. 3.53% THC, $p=0.007$ for placebo vs 1.29% THC; $p>0.05$ 1.29% THC vs. 3.53% THC). Both strengths of marijuana significantly decreased pain intensity, unpleasantness, sharpness, and deepness on NPS, as well as pain ratings on the PGIC, compared to placebo. These effects on pain were maximal with cumulative dosing over the course of the study session, with maximal effects at 180 minutes. There were no effects of marijuana compared to placebo on measures of allodynia or thermal pain. Subjects correctly identified the study treatment 63% of the time for placebo, 61% of the time for 1.29% THC, and 89% of the time for 3.53% THC.

On subjective measures, marijuana produced dose-dependent increases compared to placebo on ratings for: any drug effect, good drug effect, drug liking, high, stoned, sedated, confused, and hungry. Both strengths of marijuana produced similar increases in drunk or impaired compared to placebo. In contrast, desire for drug was rated as higher for the 1.29% THC marijuana compared to the 3.53% THC marijuana. There were no changes compared to placebo for bad effect, nauseous, anxiety, feeling down or any of the bipolar mood assessments. There was dose-dependent impairment on learning and memory from marijuana compared to placebo, but similar effects between the two strengths of marijuana on attention.

The authors conclude that vaporization of relatively low doses of marijuana can produce improvements in analgesia in neuropathic pain patients, especially when patients are allowed to titrate their exposure. However, this individualization of doses may account for the general lack of difference between the two strengths of marijuana. No data were presented regarding the total amount of THC consumed by each subject, so it is difficult to determine a proper dose-response evaluation. Additional limitations of this study are the inclusion of subjects with many forms of neuropathic pain and maintenance of subjects on other analgesic medication while being tested with marijuana. These limitations make it difficult to conclude that marijuana has analgesic properties on its own. It is also difficult to determine if any particular subset of neuropathic pain conditions would benefit specifically from marijuana administration. However, the study produced positive results suggesting that marijuana should be studied further as an adjunct treatment for uncontrolled neuropathic pain.

3.2 Appetite Stimulation in HIV

Two randomized, double-blind, placebo-controlled Phase 2 studies examined the effects of smoked marijuana on appetite in HIV-positive subjects (Haney et al., 2005; Haney et al., 2007). Table 2 of the Appendix summarizes both studies.

The first study, conducted by **Haney et al. (2005)** is entitled "Dronabinol and marijuana in HIV+ marijuana smokers: acute effects on caloric intake and mood." The subjects were 30 HIV-positive patients who were maintained on two

antiretroviral medications and either had clinically significant decreases in lean muscle mass[8] (low-BIA group, n=15) or normal lean muscle mass (normal-BIA group, n=15). All subjects had a history of smoking marijuana at least twice weekly for 4 weeks prior to entry into the study. On average, individuals had smoked 3 marijuana cigarettes per day, 5-6 times per week for 10-12 years.

Subjects participated in 8 sessions that tested the acute effects of 0, 10, 20, and 30 mg dronabinol oral capsules and marijuana cigarettes with 0%, 1.8%, 2.8%, and 3.9% THC concentration by weight, using a double-dummy design (with only one active drug per session). The doses of dronabinol are higher than those doses typically prescribed for appetite stimulation in order to help preserve the blinding. There was a one-day washout period between test sessions.

Marijuana was administered using a standardized cued procedure: (1) "light the cigarette" (30 seconds), (2) "prepare" (5 seconds), (3) "inhale" (5 seconds), (4) "hold smoke in lungs" (10 seconds), and (5) "exhale." Each subject smoked three puffs in this manner, with a 40-second interval between each puff.

Caloric intake was used as a surrogate measure for weight gain. Subjects received a box containing a variety of food and beverage items and were told to record consumption of these items following that day's administration of the test drug. Subjective measures included 0-100 point VAS for feel drug effect, good effect, bad effect, take drug again, drug liking, hungry, full, nauseated, thirsty, desire to eat. Neurocognitive measures and vital signs were monitored.

The low BIA group consumed significantly more calories in the 1.8% and 3.9% THC marijuana conditions ($p<0.01$) and the 10, 20, and 30 mg dronabinol conditions ($p<0.01$) compared with the placebo condition. In contrast, in the normal BIA group, neither marijuana nor dronabinol significantly affected caloric intake. This lack of effect may be accountable, however, by the fact that this group consumed approximately 200 calories more than the low BIA group under baseline conditions.

Ratings of high and good drug effect were increased by all drug treatments in both the low-BIA and normal-BIA groups, except in response to the 10 mg dose of dronabinol. The 3.9% THC marijuana increased ratings of good drug effect, drug liking and desire to smoke again compared with placebo. Ratings of sedation were increased in both groups by 10 and 30 mg dronabinol, and in the normal BIA group by the 2.8% THC marijuana. Ratings of stimulation were increased in the normal BIA group by 2.8% and 3.9% THC marijuana and by 20 mg dronabinol. Increases in ratings of forgetfulness, withdrawn, dreaming, clumsy, heavy limbs, heart pounding, jittery, and decreases in ratings of energetic, social, and talkative were reported in the normal BIA group with 30 mg dronabinol.

[8]Lean muscle mass was assessed using bioelectrical impedance analysis (BIA). The low-BIA group was classified with having <90% BIA, and the normal-BIA group was classified with having >90% BIA

There were no significant changes in vital signs or performance on neurocognitive measures in response to marijuana. Notably, the time course of subjective effects peaked quickly and declined thereafter for smoked marijuana, while oral dronabinol responses took longer to peak and persisted longer. Additionally, marijuana but not dronabinol produced dry mouth and thirst.

In general, AEs reported in this study were low in both drug conditions for both subject groups. In the low BIA group, nausea was reported by one subject in both the 10 and 20 mg dronabinol conditions, while an uncomfortable level of intoxication was produced by the 30 mg dose in two subjects. There were no AEs reported in this group following marijuana at any dose. In the normal BIA group, the 30 mg dose of dronabinol produced an uncomfortable level of intoxication in three subjects and headache in one subject, while the 3.9% marijuana produced diarrhea in one subject.

The authors conclude that smoked marijuana can acutely increase caloric intake in low BIA subjects without significant cognitive impairment. However, it is possible that the low degree of cognitive impairment reported in this study may reflect the development of tolerance to cannabinoids in this patient population, since all individuals had current histories of chronic marijuana use. Additional limitations in this study include not utilizing actual weight gain as a primary measure. However, the study produced positive results suggesting that marijuana should be studied further as a treatment for appetite stimulation in HIV patients.

A second study conducted by **Haney et al. (2007)** is entitled "Dronabinol and marijuana in HIV-positive marijuana smokers: Caloric intake, mood, and sleep." The design of this study was nearly identical to the one conducted by this laboratory in 2005 (see above), but there was no stratification of subjects by BIA. The subjects were 10 HIV-positive patients who were maintained on two antiretroviral medications and had a history of smoking marijuana at least twice weekly for 4 weeks prior to entry into the study. On average, individuals had smoked 3 marijuana cigarettes per day, 5 times per week for 19 years.

Subjects participated in 8 sessions that tested the acute effects of 0, 5 and 10 mg dronabinol oral capsules and marijuana cigarettes with 0, 2.0% and 3.9% THC concentration by weight, using a double-dummy design (with 4 sessions involving only one active drug and 4 interspersed placebo sessions). Both drug and placebo sessions lasted for 4 days each, with active drug administration occurring 4 times per day (every 4 hours). Testing occurred in two 16-day inpatient stays. In the intervening outpatient period, subjects were allowed to smoke marijuana prior to re-entry to the study unit for the second inpatient stay.

Marijuana was administered using a standardized cued procedure: (1) "light the cigarette" (30 seconds), (2) "prepare" (5 seconds), (3) "inhale" (5 seconds), (4) "hold smoke in lungs" (10 seconds), and (5) "exhale." Each subject smoked three puffs in this manner, with a 40-second interval between each puff.

Caloric intake was used as a surrogate measure for weight gain, but subjects were also weighed throughout the study (a measure which was not collected in the 2005 study by this group). Subjects received a box containing a variety of food and beverage items and were told to record consumption of these items following that day's administration of the test drug. Subjective measures included 0-100 point VAS for drug effect, good effect, bad effect, take drug again, drug liking, hungry, full, nauseated, thirsty, desire to eat. Neurocognitive measures and vital signs were monitored. Sleep was assessed using both the Nightcap sleep monitoring system and selected VAS measures related to sleep.

Both 5 and 10 mg dronabinol ($p < 0.008$) and 2.0% and 3.9% THC marijuana ($p < 0.01$) dose-dependently increased caloric intake compared with placebo. This increase was generally accomplished through increases in incidents of eating, rather than an increase in the calories consumed in each incident. Subjects also gained similar amounts of weight after the highest dose of each cannabinoid treatment: 1.2 kg (2.6 lbs) after 4 days of 10 mg dronabinol, and 1.1 kg (2.4 lbs) after 4 days of 3.9% THC marijuana. The 3.9% THC marijuana dose also increased the desire to eat and ratings of hunger.

Ratings of good drug effect, high, drug liking, and desire to smoke again were significantly increased by 10 mg dronabinol and 2.0% and 3.9% THC marijuana doses compared to placebo. Both marijuana doses increased ratings of stimulated, friendly, and self-confident. The 10 mg dose of dronabinol increased ratings of concentration impairment, and the 2.0% THC marijuana dose increased ratings of anxious. Dry mouth was induced by 10 mg dronabinol (10 mg) and 2.0% THC marijuana. There were no changes in neurocognitive performance or objective sleep measures from administration of either cannabinoid. However, 3.9% THC marijuana increased subjective ratings of sleep.

The authors conclude that both dronabinol and smoked marijuana increase caloric intake and produce weight gain in HIV-positive patients. However, it is possible that the low degree of cognitive impairment reported in this study may reflect the development of tolerance to cannabinoids in this subject population, since all individuals had current histories of chronic marijuana use. This study produced positive results suggesting that marijuana should be studied further as a treatment for appetite stimulation in HIV patients.

3.3 Spasticity in Multiple Sclerosis

Only one randomized, double-blind, placebo-controlled Phase 2 study examined the effects of smoked marijuana on spasticity in MS.

This study was conducted by **Corey-Bloom et al. (2012)** and is entitled "Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial." The subjects were 30 patients with MS-associated spasticity and had moderate increase in tone (score ≥ 3 points on the modified Ashworth scale).

Participants were allowed to continue other MS medications, with the exception of benzodiazepines. Of the 30 subjects, 80% had a history of marijuana use and 33% had used marijuana within the previous year.

Subjects participated in two 3-day test sessions, with an 11-day washout period. During each test session they smoked a 4.0% THC marijuana cigarette once per day or a placebo cigarette once per day. Smoking occurred through a standardized cued-puff procedure: (1) inhalation for 5 seconds, (2) breath-hold and exhalation for 10 seconds, (3) pause between puffs for 45 seconds. Subjects completed an average of four puffs per cigarette.

The primary outcome measure was change in spasticity on the modified Ashworth scale. Additionally, subjects were assessed using a VAS for pain, a timed walk, and cognitive tests (Paced Auditory Serial Addition Test) and AEs.

Treatment with 4.0% THC marijuana reduced subject scores on the modified Ashworth scale by an average of 2.74 points more than placebo ($p < 0.0001$) and reduced VAS pain scores compared to placebo ($p=0.008$). Scores on the cognitive measure decreased by 8.7 points more than placebo ($p=0.003$). However, marijuana did not affect scores for the timed walk compared to placebo. Marijuana increased the rating of feeling high compared to placebo.

Seven subjects did not complete the study due to adverse events (two subjects felt uncomfortably "high," two had dizziness, and one had fatigue). Of those seven subjects who withdrew, five had little or no previous experience with marijuana. When the data were re-analyzed to include these drop-out subjects, with the presumption they did not have a positive response to treatment, the effect of marijuana was still significant on spasticity.

The authors conclude that smoked marijuana had usefulness in reducing pain and spasticity associated with MS. It is concerning that marijuana-naïve subjects dropped out of the study because they were unable to tolerate the psychiatric AEs induced by marijuana. The authors suggest that future studies should examine whether different doses can result in similar beneficial effects with less cognitive impact. However, the current study produced positive results suggesting that marijuana should be studied further as an adjunct treatment for spasticity in MS patients.

3.4 Asthma

Tashkin et al. (1974) examined bronchodilation in 10 subjects with bronchial asthma in the study entitled "Acute Effects of Smoked Marijuana and Oral Δ^9-Tetrahydrocannabinol on Specific Airway Conductance in Asthmatic Subjects." The study was a double-blind, placebo-controlled, crossover design. All subjects were clinically stable at the time of the study; four subjects were symptom free, and six subjects had chronic symptoms of mild to moderate severity. Subjects were tested with

0.25ml of isoproterenol HCl prior to the study to ensure they responded to bronchodilator medications. Subjects were not allowed to take bronchodilator medication within 8 hours prior to the study. Previous experience with marijuana was not required for participation in the study, but 7 of the 10 subjects reported previous use of marijuana at a rate of less than one marijuana cigarette per month. No subjects reported marijuana use within 7 days of the study.

The study consisted of four test sessions with an interval of at least 48 hours between sessions. On two test sessions subjects smoked 7 mg/kg of body weight of either marijuana, with 2% THC concentration by weight, or placebo marijuana. During the other two test sessions, subjects ingested capsules with either 15mg of synthetic THC or placebo. Marijuana was administered using a uniform smoking technique: subjects inhaled deeply for 2-4 seconds, held smoke in lungs for 15 seconds, and resumed normal breathing for approximately 5 seconds. The author did not provide a description of the number of puffs taken at any smoking session. The authors state that the smoking procedure was repeated until the cigarette was consumed, which took approximately 10 minutes.

The outcome measure used was specific airway conductance (SGaw), as calculated using measurements of thoracic gas volume (TGV) and airway resistance (Raw) using a variable-pressure body plethysmograph. Additionally, an assessment of degree of intoxication was administered only to those subjects reporting previous marijuana use. This assessment consisted of subjects rating "how 'high' they felt" on a scale of 0-7, 7 representing "the 'highest' they had ever felt after smoking marijuana".

Marijuana produced a significant increase of 33-48% in average SGaw compared to both baseline and placebo ($P < 0.05$). This significant increase in SGaw lasted for at least 2 hours after administration. The average TGV significantly decreased by 4-13% compared to baseline and placebo ($P < 0.05$). The author stated that all subjects reported feelings of intoxication after marijuana administration.

The authors conclude that marijuana produced bronchodilation in clinically stable asthmatic subjects with minimal to moderate bronchospasms. Study limitations include: inclusion of subjects with varying severity of asthmatic symptoms, use of SGaw to measure lung responses to marijuana administration, and administration of smoke to asthmatic subjects. Smoke delivers a number of harmful substances and is not an optimal delivery symptom, especially for asthmatic patients. Forced expiratory volume (FEV1) via spirometry is the gold standard to assess changes in lung function, pre and post asthma treatment, by pharmacotherapy. SGaw has been shown to be a valid tool in bronchoconstriction lung assessment; however, since the FEV1 method was not utilized, it is unclear whether these results would correlate if the FEV1 method had been employed.

3.5 Glaucoma

Two randomized, double-blind, placebo-controlled Phase 2 clinical studies examined smoked marijuana in glaucoma (**Crawford and Merritt, 1979; Merritt et al., 1980**). In both studies, intraocular pressure (IOP) was significantly reduced 30 minutes after smoking marijuana. Maximal effects occurred 60-90 minutes after smoking, with IOP returning to baseline within 3-4 hours. These two studies were included in the 1999 IOM report on the medical uses of marijuana. Because our independent analysis of these studies concurred with the conclusions from the 1999 IOM report, these studies will not be discussed in further detail in this review. No recent studies have been conducted examining the effect of inhaled marijuana on IOP in glaucoma patients. This lack of recent studies may be attributed to the conclusions made in the 1999 IOM report that while cannabinoids can reduce IOP, the therapeutic effects require high doses that produce short-lasting responses, with a high degree of AEs. This high degree of AEs means that the potential harmful effects of chronic marijuana smoking may outweigh its modest benefits in the treatment of glaucoma.

3.6 Conclusions

Of the eleven randomized, double-blind, placebo-controlled Phase 2 clinical studies that met the criteria for review (see sections 2.2 and 2.3), ten studies administered marijuana through smoking, while one study utilized marijuana vaporization. In these eleven studies, there were five different therapeutic indications: five examined chronic neuropathic pain, two examined appetite stimulation in HIV patients, two examined glaucoma, one examined spasticity in MS, and one examined asthma.

There are limited conclusions that can be drawn from the data in these published studies evaluating marijuana for the treatment of different therapeutic indications. The analysis relied on published studies, thus information available about protocols, procedures, and results were limited to documents published and widely available in the public domain. The published studies on medical marijuana are effectively proof-of-concept studies. Proof-of-concept studies provide preliminary evidence on a proposed hypothesis regarding a drug's effect. For drugs under development, the effect often relates to a short-term clinical outcome being investigated. Proof-of-concept studies serve as the link between preclinical studies and dose ranging clinical studies. Therefore, proof-of-concept studies are not sufficient to demonstrate efficacy of a drug because they provide only preliminary information about the effects of a drug. Although these studies do not provide evidence that marijuana is effective in treating a specific, recognized disorder, these studies do support future larger well-controlled studies to assess the safety and efficacy of marijuana for a specific medical indication. Overall, the conclusions below are preliminary, based on very limited evidence.

3.6.1 Conclusions for Chronic Neuropathic Pain

In subjects with chronic neuropathic pain who are refractory to other pain treatments, five proof-of-concept studies produced positive results regarding the use of smoked marijuana for analgesia. However, the subjects in these studies continued to use their current analgesic drug regime, and thus no conclusions can be made regarding the potential efficacy of marijuana for neuropathic pain in patients not taking other analgesic drugs. Subjects also had numerous forms of neuropathic pain, making it difficult to identify whether a specific set of symptoms might be more responsive to the effects of marijuana. It is especially concerning that some marijuana-naïve subjects had intolerable psychiatric responses to marijuana exposure at analgesic doses.

3.6.2 Conclusions for Appetite Stimulation in HIV

In subjects who were HIV-positive, two proof-of-concept studies produced positive results with the use of both dronabinol and smoked marijuana to increase caloric intake and produce weight gain in HIV-positive patients. However, the amount of THC in the marijuana tested in these studies is four times greater than the dose of dronabinol typically tested for appetite stimulation (10 mg vs. 2.5 mg; Haney et al., 2005). Thus, it is possible that the low degree of AEs reported in this study may reflect the development of tolerance to cannabinoids in this patient population, since all individuals had current histories of chronic marijuana use. Thus, individuals with little prior exposure to marijuana may not respond similarly and may not be able to tolerate sufficient marijuana to produce appetite stimulation.

3.6.3 Conclusions for Spasticity in MS

In subjects with MS, a proof of concept study produced positive results using smoked marijuana as a treatment for pain and symptoms associated with treatment-resistant spasticity. The subjects in this study continued to take their current medication regiment, and thus no conclusions can be made regarding the potential efficacy of marijuana when taken on its own. It is also concerning that marijuana-naïve subjects dropped out of the study because they were unable to tolerate the psychiatric AEs induced by marijuana. The authors suggest that future studies should examine whether different doses can result in similar beneficial effects with less cognitive impact.

3.6.4 Conclusions for Asthma

In subjects with clinically stable asthma, a proof of concept study produced positive results of smoked marijuana producing bronchodilation. However, in this study marijuana was administered at rest and not while experiencing bronchospasms. Additionally, the administration of marijuana through smoking introduces harmful and irritating substances to the subject, which is undesirable especially in asthmatic patients.

Thus the results suggest marijuana may have bronchodilator effects, but it may also have undesirable adverse effects in subjects with asthma.

3.6.5 Conclusions for Glaucoma

As noted in Sections 3.5, the two studies that evaluated smoked marijuana for glaucoma were conducted decades ago, and they have been thoroughly evaluated in the 1999 IOM report. The 1999 IOM report concludes that while the studies with marijuana showed positive results for reduction in IOP, the effect is short-lasting, requires a high dose, and is associated with many AEs. Thus, the potential harmful effects may outweigh any modest benefit of marijuana for this condition. We agree with the conclusions drawn in the 1999 IOM report.

3.7 Design Challenges for Future Studies

The positive results reported by the studies discussed in this review support the conduct of more rigorous studies in the future. This section discusses methodological challenges that have occurred in clinical studies with smoked marijuana. These design issues should be addressed when larger-scale clinical studies are conducted to ensure that valid scientific data are generated in studies evaluating marijuana's safety and efficacy for a particular therapeutic use.

3.7.1 Sample Size

The ability for results from a clinical study to be generalized to a broader population is reliant on having a sufficiently large study sample size. However, as noted above, all of the 11 studies reviewed in this document were early Phase 2 proof of concept studies for efficacy and safety. Thus, the sample sizes used in these studies were inherently small, ranging from 10 subjects per treatment group (Tashkin et al., 1974; Haney et al., 2007) to 25 subjects per treatment group (Abrams et al., 2007). These sample sizes are statistically inadequate to support a showing of safety or efficacy. FDA's recommendations about sample sizes for clinical trials can be found in the guidance for industry *E9 Statistical Principles for Clinical Trials (1998).*[9] For example, "the number of subjects in a clinical trial should always be large enough to provide a reliable answer to the questions addressed. This number is usually determined by the primary objective of the trial. The method by which the sample size is calculated should be given in the protocol, together with the estimates of any quantities used in the calculations (such as variances, mean values, response rates, event rates, difference to be detected)" (p. 21). Other clinical FDA guidances for industry[10] may also contain recommendations regarding the appropriate number of subjects that should be investigated for a specific medical indication.

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[9] *E9 Statistical Principles for Clinical Trials* can be found at:
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073137.pdf

[10] Other guidances for industry can be found at:
www.fda.gov/Drugs/GuidanceComplianceRegulatory Information/Guidances/ ucm064981.htm

3.7.2 Marijuana Dose Standardization

Dose standardization is critical for any clinical study in order to ensure that each subject receives a consistent exposure to the test drug. The 2004 guidance for industry entitled *Botanical Drug Products*[11] provides specific information on the development of botanical drug products. Specifically, this guidance includes information about the need for well-characterized and consistent chemistry for the botanical plant product and for consistent and reliable dosing. Specifically for marijuana studies, dose standardization is important because if marijuana leads to plasma levels of cannabinoids that are significantly different between subjects, this variation may lead to differences in therapeutic responsivity or in the prevalence of psychiatric AEs.

In most marijuana studies discussed in this review, investigators use a standardized cued smoking procedure. In this procedure, a subject is instructed to inhale marijuana smoke for 5 seconds, hold the smoke in the lungs for 10 seconds, exhale and breathe normally for 40 seconds. This process is repeated to obtain the desired dose of the drug. However, this procedure may not lead to equivalent exposure to marijuana and its constituent cannabinoids, based on several factors:

- Intentional or unintentional differences in the depth of inhalation may change the amount of smoke in the subject's lungs.
- Smoking results in loss from side stream smoke, such that the entire dose is not delivered to the subject.
- There may be differences in THC concentration along the length of a marijuana cigarette. According to Tashkin et al. (1991), the area of the cigarette closest to the mouth tends to accumulate a higher concentration of THC, but this section of the cigarette is not smoked during a study.

For example, Wilsey et al. (2008) used this standardized smoking procedure. The reported mean (range) of marijuana cigarettes consumed was 550 mg (200-830mg) for the low strength marijuana (3.5% THC) and 490 mg (270-870mg) for the high strength marijuana (7% THC). This wide range of amounts of marijuana cigarette smoked by the individual subjects, even with standardized smoking procedure and controlled number of puffs, supports the issues with delivering consistent doses with smoke marijuana.

In other marijuana studies that do not use a cued smoking procedure, subjects are simply told to smoke the marijuana cigarette over a specific amount of time (usually 10 minutes) without further instruction (Crawford and Merritt, 1979; Merritt et al., 1980; Ellis et al., 2009). The use of a nonstandardized procedure may lead to non-equivalent exposures to marijuana and its constituent

[11] *Botanical Drug Products* can be found at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070491.pdf.

cannabinoids between subjects because of additional factors that are not listed above, such as:

- Differences in absorption and drug response if subjects (especially marijuana-naïve ones) are not instructed to hold marijuana smoke in their lungs for a certain period of time.
- Prolonged periods between puffs may increase loss to side stream smoke.
- Subjects may attempt to smoke the marijuana cigarette in the way they would smoke a tobacco cigarette, which relies primarily on short, shallow puffs.

In both standardized and non-standardized smoking procedures, subjects may seek to control the dose of THC through self-titration (Crawford and Merritt, 1979; Merritt et al., 1980; Tashkin et al., 1974; Abrams et al., 2007; Ellis et al., 2009). Self-titration involves an individual moderating the amount of marijuana smoke inhaled over time in order to obtain a preferred level of psychoactive or clinical response. The ability of an individual to self-titrate by smoking is one reason given by advocates of "medical marijuana" in support of smoking of marijuana rather than through its ingestion via edibles. However, for research purposes, self-titration interferes with the ability to maintain consistent dosing levels between subjects, and thus, valid comparisons between study groups.

All of these factors can make the exact dose of cannabinoids received by a subject in a marijuana study difficult to determine with accuracy. Testing whether plasma levels of THC or other cannabinoids are similar between subjects following the smoking procedure would establish whether the procedure is producing appropriate results. Additionally, studies could be conducted to determine if vaporization can be used to deliver consistent doses of cannabinoids from marijuana plant material. Specifically, vaporization devices that involve the collection of vapors in an enclosed bag or chamber may help with delivery of consistent doses of marijuana. Thus, more information could be collected on whether vaporization is comparable to or different than smoking in terms of producing similar plasma levels of THC in subjects using identical marijuana plant material.

3.7.3 Acute vs. Chronic Therapeutic Marijuana Use

The studies that were reviewed administered the drug for short durations lasting no longer than 5 days (Abrams et al., 2007; Ellis et al., 2009; Ware et al., 2010). Thus all studies examined the short-term effect of marijuana administration for therapeutic purposes. However, many of the medical conditions that have been studied are persistent or expected to last the rest of a patient's life. Therefore, data on chronic exposure to smoked marijuana in clinical studies is needed. In this way, more information will be available regarding whether tolerance,

physical dependence, or specific adverse events develop over the course of time with continuing use of therapeutic marijuana.

3.7.4 Smoking as a Route of Administration

As has been pointed out by the IOM and other groups, smoking is not an optimum route of administration for marijuana-derived therapeutic drug products, primarily because introducing the smoke from a burnt botanical substance into the lungs of individuals with a disease state is not recommended when their bodies may be physically compromised. The 1999 IOM report on medicinal uses of marijuana noted that alternative delivery methods offering the same ability of dose titration as smoking marijuana will be beneficial and may limit some of the possible long-term health consequences of smoking marijuana. The primary alternative to smoked marijuana is vaporization, which can reduce exposure to combusted plant material containing cannabinoids. The only study to use vaporization as the delivery method was Wilsey et al. (2013). The results from Wilsey et al. (2013) showed a similar effect of decreased pain as seen in the other studies using smoking as the delivery method (Ware et al., 2010; Wilsey et al., 2008). This similar effect of decrease pain supports vaporization as a possibly viable route to administer marijuana in research, while potentially limiting the risks associated with smoking.

3.7.5 Difficulty in Blinding of Drug Conditions

An adequate and well-controlled clinical study involves double-blinding, where both the subjects and the investigators are unable to tell the difference between the test treatments (typically consisting of at least a test drug and placebo) when they are administered. All of the studies reviewed in this document administered study treatments under double-blind conditions and thus were considered to have an appropriate study design.

However, even under the most rigorous experimental conditions, blinding can be difficult in studies with smoked marijuana because the rapid onset of psychoactive effects readily distinguishes active from placebo marijuana. The presence of psychoactive effects also occurs with other drugs. However, most other drugs have a similar psychoactive effect with substances with similar mechanisms of actions. These substances can be used as positive controls to help maintain blinding to the active drug being tested. Marijuana on the other hand, has a unique set of psychoactive effects which makes the use of appropriate positive controls difficult (Barrett et al., 1995). However, two studies did use Dronabinol as a positive control drug to help maintain blinding (Haney et al., 2005; Haney et al., 2007).

When blinding is done using only placebo marijuana, the ability to distinguish active from placebo marijuana may lead to expectation bias and an alteration in perceived responsivity to the therapeutic outcome measures. With marijuana-experienced subjects, for example, there may be an early recognition of the more

subtle cannabinoid effects that can serve as a harbinger of stronger effects, which is less likely to occur with marijuana-naïve subjects. To reduce this possibility, investigators have tested doses of marijuana other than the one they were interested in experimentally to maintain the blind (Ware et al., 2010).

Blinding can also be compromised by differences in the appearance of marijuana plant material based on THC concentration. Marijuana with higher concentrations of THC tends to be heavier and seemingly darker, with more "tar-like" substance. Subjects who have experience with marijuana have reported being able to identify marijuana from placebo cigarettes by sight alone when the plant material in a cigarette was visible (Tashkin et al., 1974; Ware et al., 2010). Thus, to maintain a double-blind design, many studies obscure the appearance of plant material by closing both ends of the marijuana cigarette and placing it in in an opaque plastic tube.

While none of these methods to secure blinding may be completely effective, it is important to reduce bias as much as possible to produce consistent results between subjects under the same experimental conditions.

3.7.6 Prior Marijuana Experience

Marijuana use histories in test subjects may influence outcomes, related to both therapeutic responsivity and psychiatric AEs. Marijuana-naïve subjects may also experience a marijuana drug product as so aversive that they would not want to use the drug product. Thus, subjects' prior experience with marijuana may affect the conduct and results of studies.

Most of the studies reviewed in this document required that subjects have a history of marijuana use (see tables in Appendix that describe specific requirements for each study). However, in studies published in the scientific literature, the full inclusion criteria with regard to specific amount of experience with marijuana may not be provided. For those studies that do provide inclusion criteria, acceptable experience with marijuana can range from once in a lifetime to use multiple times a day.

The varying histories of use might affect everything from scores on adverse event measures, safety measures, or efficacy measures. Additionally, varying amounts of experience can impact cognitive effect measures assessed during acute administration studies. For instance, Schreiner and Dunn (2012) contend cognitive deficits in heavy marijuana users continue for approximately 28 days after cessation of smoking. Studies requiring less than a month of abstinence prior to the study may still see residual effects of heavy use at baseline and after placebo marijuana administration, thus showing no significant effects on cognitive measures. However, these same measurements in occasional or naïve marijuana users may demonstrate a significant effect after acute marijuana administration. Therefore, the amount of experience and the duration of abstinence of marijuana use are important to keep in mind when analyzing results

for cognitive and other adverse event measures. Lastly, a study population with previous experience with marijuana may underreport the incidence and severity of adverse events. Because most studies used subjects with prior marijuana experience, we are limited in our ability to generalize the results, especially for safety measures, to marijuana-naïve populations.

Of the 11 studies reviewed in this document, 5 included both marijuana-naïve and marijuana-experienced subjects (Corey-Bloom et al., 2012; Ellis et al., 2009; Ware et al., 2010; Merritt et al., 1980; Tashkin et al., 1974). Since the number of marijuana-naïve subjects in these studies was low, it was not possible to conduct a separate analysis compared to experienced users. However, systematically evaluating the effect of marijuana experience on study outcomes is important, since many patients who might use a marijuana product for a therapeutic use will be marijuana-naïve.

Research shows that marijuana-experienced subjects have a higher ability to tolerate stronger doses of oral dronabinol than marijuana-naïve subjects (Haney et al., 2005). Possibly, this increased tolerance is also the case when subjects smoke or vaporize marijuana. Thus, studies could be conducted that investigate the role of marijuana experience in determining tolerability of and responses to a variety of THC concentrations in marijuana.

3.7.7 Inclusion and Exclusion Criteria

For safety reasons, all clinical studies have inclusion and exclusion criteria that restrict the participation of individuals with certain medical conditions. For studies that test marijuana, these criteria may be based on risks associated with exposure to smoked material and the effects of THC. Thus, most studies investigating marijuana require that subjects qualify for the study based on restrictive symptom criteria such that individuals do not have other symptoms that may be known to interact poorly with cannabinoids.

Similarly, clinical studies with marijuana typically exclude individuals with cardiac or pulmonary problems, as well as individuals with psychiatric disorders. These exclusion criteria are based on the well-known effects of marijuana smoke to produce increases in heart rate and blood pressure, lung irritation, and the exacerbation of psychiatric disturbances in vulnerable individuals. Although these criteria are medically reasonable for research protocols, it is likely that future marijuana products will be used in patients who have cardiac, pulmonary, or psychiatric conditions. Thus, individuals with these conditions should be evaluated, whenever possible.

Additionally, all studies reviewed in this document allowed the subjects to continue taking their current regimen of medications. Thus all results evaluated marijuana as an adjunct treatment for each therapeutic indication.

3.7.8 Number of Female Subjects

A common problem in clinical research is the limited number of females who participate in the studies. This problem is present in the 11 studies reviewed in this document, in which one study did not include any female subjects (Ellis et al., 2009) and three studies had a low percentage of female subjects (Abrams et al., 2007; Haney et al., 2005; Haney et al., 2007). However, each of these four studies investigated an HIV-positive patient population, where there may have been a larger male population pool from which to recruit compared to females.

Since there is some evidence that the density of cannabinoid receptor type 1 (CB1) receptors in the brain may vary between males and females (Crane et al., 2012), there may be differing therapeutic or subjective responsivity to marijuana. Studies using a study population that is equal parts male and female may show whether and how the effects of marijuana differ between male and female subjects.

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Appendix (Tables)

Table 1: Randomized, controlled, double-blind trials examining smoked marijuana in treatment of neuropathic pain

Author & Date *Indication*	Subjects (n) completed/randomized Subject characteristics	Drugs Admin. Methods	Study Type *Duration*	Primary Outcome Measure	Primary Outcome Measure Results	Adverse events/AEs
Abrams et al. (2007) *HIV-Sensory Neuropathy; Neuropathic Pain*	Marijuana Group: 25/27 22 males 5 females Placebo Group: 25/28 26 males 2 females Inclusion Criteria: -documented HIV -documented HIV-SN -pain score ≥30mm VAS -prior marijuana use of six or more times in lifetime Previous Marijuana Experience: -marijuana group: 21 current users -placebo group: 19 current users Exclusion Criteria: -substance abuse (including tobacco) -family history of neuropathy due to causes not HIV related -use of isoniazid, dapsone, or metronidazole within 8 weeks of enrollment	NIDA marijuana, smoked 0%, 3.65% THC Smoking Procedure: -signal light cued smoking of marijuana cigarette with each puff consisting of: 1) 5s inhale smoke, 2) 10s hold smoke in lungs 3) 40s exhale and breath normally 4) repeat procedure for desired number of puffs # of puffs not specified, only specified that subjects smoked the entire marijuana/placebo cigarette On 1st and last day of intervention period BID. For all other days TID	Parallel Group *5-day treatment period*	VAS daily pain score	-52% of the marijuana group showed >30% decrease in pain score compared to 24% of placebo group. -Marijuana group had significantly greater reduction in daily pain score than placebo group. -NNT=3.6	-Rating for adverse events of anxiety, sedation, disorientation, confusion, and dizziness were significantly higher in the marijuana group compared to placebo group. -Marijuana and placebo groups showed a reduction in total mood disturbance on POMS. AEs: -1 grade 3 dizziness in marijuana group -2 grade 3 anxiety. 1 in each group.
Ellis et al. (2009) *HIV Sensory*	28/34 28 males Inclusion Criteria:	NIDA marijuana, smoked 0%, 1%, 2%, 4%, 6%, 8% THC	Crossover Dose-titration (on	Pain magnitude on DDS	-Pain reduction was significantly greater after marijuana compared to placebo.	-Mood disturbance, quality of life, and psychical disability improved for both marijuana and placebo. -Moderate to severe adverse events

Author & Date *Indication*	Subjects (n) completed/randomized Subject characteristics	Drugs Admin. Methods	Study Type *Duration*	Primary Outcome Measure	Primary Outcome Measure Results	Adverse events/AEs
Neuropathy; Neuropathic Pain	-documented HIV -documented neuropathic pain refractory to ≥2 analgesics -pain score ≥5 on pain intensity subscale of DDS Previous Marijuana Experience: -27 subjects had previous experience -63% of subjects had no exposure for >1 year before study Exclusion Criteria: -current DSM-IV substance abuse disorder -lifetime history of dependence on marijuana -previous psychosis with or intolerance to cannabinoids -concurrent use of approved cannabinoid medications -positive UDS for cannabinoids during wash-in week -serious medical conditions that affect safety -alcohol or drug dependence within 12 months of study	Smoking Procedures: - Verbally cued smoking of marijuana cigarette with each puff consisting of: 1) 5s inhale smoke, 2) 10s hold smoke in lungs 3) 40s exhale and breath normally 4) repeat procedure for desired number of puffs -unknown number of puffs QID	1st day) *2, 5-day treatment phase, with 2-week washout period*		-NNT=3.5	were more common with marijuana than placebo. -HIV disease parameters did not differ for marijuana or placebo. -Adverse events included: concentration difficulties, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation, and thirst. These adverse events were more frequent in marijuana compared to placebo. Withdrawals for drug related reasons: -1 cannabis-naïve subject had acute cannabis-induced psychosis -1 subjects developed an intractable smoking-related cough during marijuana administration
Wilsey et al. (2008) *Neuropathic pain; Various Causes*	32/38 20 males 18 females Inclusion Criteria: -CRPS type I, spinal cord	NIDA marijuana, smoked 0%, 3.55%, 7% THC Smoking Procedure: Verbally cued	Crossover *3, 6-hour sessions, with 3-day between*	VAS spontaneous pain intensity	-A significant decrease in pain intensity for both strengths of marijuana compared to placebo	-7% THC marijuana significantly decreased functioning on neurocognitive measures compared to placebo. -Subjective effects were greater for 7% THC marijuana than 3.55%

Author & Date *Indication*	Subjects (n) completed/randomized Subject characteristics	Drugs Admin. Methods	Study Type *Duration*	Primary Outcome Measure	Primary Outcome Measure Results	Adverse events/AEs
	injury, peripheral neuropathy, or nerve damage -previous marijuana use Previous Marijuana Experience: -median (range) time from previous exposure: 1.7 years (31 days to 30 years) -median (range) exposure duration: 2 years (1 day to 22 years). Exclusion Criteria: -no marijuana or cannabinoid medication use for 30 days prior to study; confirmed by UDS -severe depression -history of schizophrenia or bipolar depression -uncontrolled hypertension, cardiovascular disease, and pulmonary disease -active substance abuse	smoking of marijuana cigarette with each puff consisting of: 1) 5s inhale smoke, 2) 10s hold smoke in lungs 3) 40s exhale and breath normally 4) repeat procedure for desired number of puffs Cumulative dosing procedure: -escalate the number of puffs from 2 to 4 puffs over 3 smoking sessions with 1 hour between sessions TID	*sessions*			THC marijuana with significantly more ratings of good drug effect, bad drug effect, feeling high, feeling stoned, impaired, sedation, confusion, and hunger compared to placebo.
Ware et al. (2010) *Post-traumatic or postsurgical neuropathic pain*	21/23 11 males 12 females Inclusion Criteria: -neuropathic pain for ≥ 3 months caused by trauma or surgery -allodynia and hyperalgesia -pain score >4cm VAS -no marijuana use for 1 year prior to study -stable analgesic regimen	NIDA placebo; Prairie Plant System Inc. (Canada) marijuana, smoked 0%, 2.5%, 6%, 9.4% THC (25 mg of marijuana/placebo plant material was placed in opaque gelatin capsules)	Crossover *4, 5-day out-patient* treatment phase, with 9-day washout periods*	Pain intensity on 11-item NRS	-Average daily pain intensity was significantly lower after 9.4% THC compared to placebo.	-Anxiety and depression were significantly improved with 9.4% THC compared to placebo. -No significant difference between placebo and 9.4% THC for subjective effects. AEs: -248 mild AEs were reported -6 moderate AEs were reported: 2 fall, 1 increased pain, 1 numbness, 1 drowsiness, 1 pneumonia -Most frequently reported drug-

Author & Date *Indication*	Subjects (n) completed/randomized Subject characteristics	Drugs Admin. Methods	Study Type *Duration*	Primary Outcome Measure	Primary Outcome Measure Results	Adverse events/AEs
	-normal liver and renal function Previous Marijuana Experience: -18 subjects had used marijuana before Exclusion Criteria: -pain due to cancer or nociceptive causes -significant cardiac or pulmonary disease -current substance abuse or dependence (including marijuana) -history of psychotic disorders -current suicidal ideations	Smoking Procedures: -1) Break one capsule open and tip content into the bowl of a titanium pipe 2) light marijuana material 3) 5s inhale smoke 4) 10s hold smoke in lungs 5) Exhale 1 puff burned all 25 mg of plant material TID Intermediate doses were used to help maintain blinding				related AEs for 9.4% THC: headache, dry eyes, burning sensation, dizziness, numbness, and cough. Withdrawals for drug related reason: -1 subject had increased pain after 6% THC administration -1 subject tested positive for cannabinoids in urine test during placebo treatment
Wilsey et al. (2013) *Neuropathic Pain; Various Causes*	36/39 28 males 11 females Inclusion Criteria: -CRPS type I, thalamic pain, spinal cord injury, peripheral neuropathy, radiculopathy, or nerve injury -previous marijuana use Previous Marijuana Experience: - median (range) time from last exposure prior to screening: 9.6 years (1 day to 45 years) -16 current marijuana users and 23 past users	NIDA marijuana, vaporized 0%, 1.29%, 3.53% THC Smoking Procedures: - Verbally cued inhalation of vaporized material in the balloon with each puff consisting of: 1) 5s inhale vapors, 2) 10s hold vapors in lungs 3) 40s exhale and breath normally 4) repeat procedure for desired number of puffs	Crossover *3, 6-hour sessions, with at least 3 days between sessions*	VAS spontaneous pain intensity	-Number of subjects that showed a 30% reduction in pain intensity was significantly greater for both strengths of marijuana compared to placebo. -Both strengths of marijuana showed a similar significant decrease in pain compared to placebo. -NNT=3.2 for 1.29% THC marijuana vs. placebo. -NNT=2.9 for 3.53% THC marijuana vs. placebo.	-Scores for feeling stoned, feeling high, like the drug effect, feeling sedated, and feeling confused were significantly greater for 3.53% THC marijuana compared to 1.29% THC marijuana, and for both strengths of marijuana compared to placebo. -Scores for feeling drunk and feeling impaired are significantly greater in both strengths of marijuana compared to placebo. -Scores for desired more of the drug were significantly greater for 1.29% THC marijuana compared to placebo, with no significant difference seen for 3.53% THC marijuana. -3.53% THC marijuana had significantly worse performance

Author & Date *Indication*	Subjects (n) completed/randomized Subject characteristics	Drugs Admin. Methods	Study Type *Duration*	Primary Outcome Measure	Primary Outcome Measure Results	Adverse events/AEs
	-# smoked daily: 6 current users, 5 past users -# used approx. once every 2 weeks: 8 current users, 6 past users -# used once every 4 weeks or less: 2 current users, 12 past users <u>Exclusion Criteria:</u> -no marijuana or cannabinoid medication use for 30 days prior to study; confirmed by UDS -severe depression -suicidal ideations -diagnoses of serious mental illness -uncontrolled hypertension, cardiovascular disease, or chronic pulmonary disease -active substance abuse	BID Cumulative & Flexible Dosing: -1st drug admin. consisted of 4 puffs from balloon. -Followed 2 hours later by 2nd drug admin. -2nd drug admin. consisted of 4 to 8 puffs from balloon; number of puffs taken was left up to the subject so they could self-titrate to their target does, which balanced desired response and tolerance levels.				than 1.29% THC marijuana for learning and memory. -Both strengths of marijuana significantly reduced scores on attention compared to placebo.

♦Out-patient: subjects were given enough doses of marijuana/placebo to last the 5-day treatment phase, and then were sent home for the remainder of the treatment phase.
AE=Adverse Event; BID=drug administered two times per day; CRPS=complex regional pain syndrome; DDS=Descriptor Differential Scale; NIDA=National Institute of Drug Abuse; NNT=Number Needed to Treat; NRS=Numeric Rating Scale; QID=drug administered four times per day; THC=delta-9-tetrahydrocannbinol; TID=drug administered three times per day; UDS=urine drug screen; VAS=Visual Analog Scale.

Table 2: Randomized, controlled, double-blind trials examining smoked marijuana in treatment of appetite stimulation in HIV/AIDS

Author & Date *Indication*	Subjects (n) completed/randomized Subject characteristics	Drugs Admin. Methods	Study Type *Duration*	Primary Outcome Measure	Results (summary)	Adverse events/AEs
Haney et al. (2005) *HIV+ with either normal muscle mass (Normal-BIA) or clinically significant loss of muscle mass (Low-BIA)*	Low-BIA: 15/17 12 males 3 females Normal-BIA: 15/18 15 males <u>Inclusion Criteria:</u> -21-50 years of age -prescribed at least 2 antiretroviral medications -currently under the care of a physician for HIV management -medically and psychiatrically stable -smoke marijuana ≥ 2x/week for past 4 weeks <u>Previous Marijuana Experience:</u> -mean (SD) # of days/week of marijuana use: Low-BIA= 6 (2); Normal-BIA=5 (2) -mean (SD) # marijuana cigarettes/day: Low-BIA=3 (2); Normal-BIA=3 (1) -mean (SD) years of marijuana use: Low-BIA=12.2 (8.3); Normal-BIA=10.8 (2.6) <u>Exclusion Criteria:</u> -diagnosis of nutritional malabsorption, major depression, dementia,	NIDA marijuana, smoked 0%, 1.8%, 2.8%, 3.9% THC Dronabinol, oral 0, 10, 20, 30mg Double-dummy drug admin. Procedures: -only 1 active dose per session -one dronabinol/placebo capsule followed 1 hour later by marijuana/placebo smoking <u>Smoking Procedures:</u> Verbally cued smoking of marijuana cigarette with each puff consisting of: 1) 5s inhale smoke, 2) 10s hold smoke in lungs 3) 40s exhale and breath normally 4) repeat for 3 puffs per smoking session QD	Crossover *8, 7-hour session, with at least 1 day between sessions*	No primary outcome measure is specified Related outcome measure was caloric intake	-In Low-BIA all dronabinol doses and 1.8% and 3.9% THC marijuana significantly increased caloric intake compared with placebo.	-Ratings of high and good drug effect were significantly increased for all strengths of marijuana and all doses of dronabinol except 10mg dronabinol. -3.9% THC significantly increased ratings of dry mouth and thirsty compared to placebo. -Low-BIA group showed no significant adverse event ratings, and in the normal-BIA group the only significant adverse events in response to marijuana included: diarrhea after 3.9% THC marijuana. -Dronabinol had more incidences of adverse events at all doses compared to marijuana.

Author & Date *Indication*	Subjects (n) completed/randomized Subject characteristics	Drugs Admin. Methods	Study Type *Duration*	Primary Outcome Measure	Results (summary)	Adverse events/AEs
	chronic diarrhea, weakness, fever, significant pulmonary disease -an opportunistic infection within past 3 months -obesity -use of steroids within past 3 weeks -drug dependence (excluding marijuana or nicotine)					
Haney et al. (2007) *HIV+*	10 9 males 1 female Inclusion Criteria: -21-50 years of age -taking ≥ 2 antiretroviral medications -under the care of a physician for HIV management -medically and psychiatrically stable -smoke marijuana ≥ 2x/week for the past 4 weeks Previous Marijuana Experience: -mean (SD) # of days/week of marijuana use: 4.6 (0.6) -mean (SD) # marijuana cigarettes/day: 3.2 (0.8) -mean (SD) years of marijuana use: 18.6 (3.3)	NIDA marijuana, smoked 0%, 2%, 3.9% THC Dronabinol, oral 0, 5, 10mg Double-dummy drug admin. Procedures: -only 1 active dose per session -one dronabinol/placebo capsule followed 1 hour later by marijuana/placebo smoking Smoking Procedures: Light cued smoking of marijuana cigarette with each puff	Crossover *2, 16-day treatment phases, with 5-10 days between phases* *Each 16-day treatment phase consisted of 2, 4-day active drug period with 4-day placebo period between active drug periods.*	No primary outcome measure is specified Related outcome measures were Caloric Intake & Body Weight	-Both strengths of marijuana significantly increased caloric intake compared to placebo. -3.9% THC marijuana significantly increased body weight compared to placebo.	-Both strengths of marijuana significantly increased ratings of: good drug effect, high, mellow, stimulate, friendly, and self-confident. Only 2% THC marijuana significantly increased ratings of anxious. -Both strengths of marijuana significantly increased subjective measures for satisfied sleep and estimated time of sleep.

Author & Date *Indication*	Subjects (n) completed/randomized Subject characteristics	Drugs Admin. Methods	Study Type *Duration*	Primary Outcome Measure	Results (summary)	Adverse events/AEs
	Exclusion Criteria: -diagnosis of nutritional malabsorption, major depression, dementia, chronic diarrhea, weakness, fever, significant pulmonary disease -an opportunistic infection within past 3 months -obesity -use of steroids within past 3 weeks -drug dependence (excluding marijuana or nicotine)	consisting of: 1) 5s inhale smoke, 2) 10s hold smoke in lungs 3) 40s exhale and breath normally 4) repeat for 3 puffs per smoking session QID				

AE=Adverse Event; BIA=Bioelectric Impedance Analysis; NIDA=National Institute of Drug Abuse; QD=drug administered one time per day; QID=drug administered four times per day; THC=delta-9-tetrahydrocannbinol

Table 3: Randomized, controlled, double-blind trails examining smoked marijuana in treatment of spasticity in Multiple Sclerosis

Author & Date *Indication*	Subjects (n) completed/randomized Subject characteristics	Drugs Admin. Methods	Study Type *Duration*	Primary Outcome Measure	Primary Outcome Measure Results	Adverse events/AEs
Corey-Bloom et al. (2012) *Multiple Sclerosis; Spasticity*	30/37 11 males 19 females Inclusion Criteria: -documented MS -spasticity -moderate increase in tone (score ≥ 3 on modified Ashworth scale Previous Marijuana Experience: -24 subjects had previous exposure to marijuana -10 subjects used marijuana within the year Exclusion Criteria: -no marijuana smoking for ≤1 month prior to screening -psychiatric disorder (other than depression) -history of substance use -substantial neurological disease other than MS -severe or unstable medical illnesses -known pulmonary disorders -using high dose narcotic medication for pain -using benzodiazepines to control spasticity	NIDA marijuana, smoked 0%, 4% THC Smoking Procedure: smoking of marijuana cigarette with each puff consisting of: 1) 5s inhale smoke, 2) 10s hold smoke in lungs 3) 45s exhale and breath normally 4) repeat for an average of 4 puffs per smoking session QD	Crossover *2, 3-day treatment periods, with 11 day washout period*	Spasticity on the Modified Ashworth Scale	-Smoking marijuana significantly reduced spasticity scores compared to placebo	-Marijuana reduced scores on cognitive measure compared to placebo. -Marijuana significantly increased perceptions of "highness" compared to placebo Withdrawals for drug-related reasons: -2 subjects felt uncomfortably high -2 dizziness -1 fatigue

AE=Adverse Event; MS= Multiple Sclerosis; NIDA=National Institute of Drug Abuse; QD=drug administered one time per day; THC=delta-9-tetrahydrocannbinol;

Table 4: Randomized, controlled, double-blind trails examining smoked marijuana in treatment of intraocular pressure in Glaucoma

Author & Date *Indication*	Subjects (n) completed/randomized Subject characteristics	Drugs Admin. Methods	Study Type *Duration*	Primary Outcome Measure	Results (summary)	Adverse events/AEs
Crawford & Merritt (1979) *Hypertensive and Normotensive Glaucoma*	HT group: 8 4 males 4 females NT group: 8 4 males 4 females Inclusion Criteria: -documented glaucoma Previous Marijuana Experience: -all were marijuana naïve Exclusion Criteria: -coronary artery disease	NIDA marijuana, smoked 0%, 2.8% THC Smoking Procedure: -instructed to inhale 20 times deeply and retain smoke in lungs -smoke marijuana/placebo cigarette in 5 minutes QD	Crossover *4, 1-day sessions, no time between sessions*	No primary outcome measure is specified Related outcome measure was IOP	-Marijuana decreased IOP by 37-44% from baseline. -The maximal decrease in IOP was significantly greater in HT (-14mmHg) than NT (-9mmHg) after marijuana.	-Placebo marijuana increased heart rate for 10 minutes in both groups. -The maximal increase in heart rate was significantly greater in NT than HT after marijuana. -The maximal decrease in blood pressure was significantly greater in HT than NT after marijuana.
Merritt et al. (1980) *Glaucoma*	18 12 males 6 females (31 glaucoma eyes, analyzed results for each eye) Inclusion Criteria: -documented glaucoma Previous Marijuana Experience: -9 subjects had used marijuana at least once Exclusion Criteria: -cardiac, neurological, and psychiatric dysfunction	NIDA marijuana, smoked 0%, 2% THC Smoking Procedure: -None described -smoked 1 marijuana/placebo cigarette over 10-20 minutes QD	Crossover *2, 1-day sessions*	No primary outcome measure is specified Related outcome measure was IOP	-Marijuana significantly decreased IOP compared to placebo	-Marijuana significantly increased heart rate compared to placebo -Blood pressure significantly decreased after marijuana -All subjects experienced hunger, thirst, euphoria, drowsy, and feeling cold -Observed adverse events were greater in marijuana-naïve subjects than in subjects with prior marijuana experience. AEs: -5 subjects postural hypotension -8 subjects anxiety with tachycardia and palpitations

AE=Adverse Event; HT=Hypertensive; IOP=Intraocular pressure; NIDA=National Institute of Drug Abuse; NT=Normotensive; QD=drug administered one time per day; THC=delta-9-tetrahydrocannbinol

Table 5: Randomized, controlled, double-blind trails examining smoked marijuana in treatment of asthma

Author & Date *Indication*	Subjects (n) completed/randomized Subject characteristics	Drugs Admin. Methods	Study Design *Duration*	Primary Outcome Measure	Results (summary)	Adverse events/AEs
Tashkin et al. (1974) *Bronchial Asthma*	10 5 males 5 females Inclusion Criteria: -diagnosis of bronchial asthma -asthma relieved by bronchodilator medication -clinically stable Previous Marijuana Experience: -7 subjects had previous exposure to marijuana -amount of exposure <1 cigarette/month Exclusion Criteria: -no marijuana use ≤7 days of study -psychiatric illness	NIMH (NIDA) marijuana, smoked 0%, 2% THC Dronabinol, oral 0, 15mg Dosing is 7mg/kg of body weight of plant material Smoking Procedure: smoking of marijuana cigarette with each puff consisting of: 1) 2-4s deep inhale smoke, 2) 15s hold smoke in lungs 3) 5s exhale and breath normally 4) repeat till entire cigarette is smoked QD	Crossover *4, 1-day sessions, with at least 48 hours between sessions*	No primary outcome measure is specified Related outcome measure was sGaw	-Marijuana significantly increased sGaw (33-48%) compared to placebo and baseline	-Marijuana initially significantly increased pulse rate compared to placebo, and then at 90 minutes pulse rate was significantly decreased compared to baseline. -All subjects felt intoxicated after marijuana.

AE=Adverse Event; NIDA=National Institute of Drug Abuse; QD=drug administered one time per day; sGaw=Specific Airway Conductance; THC=delta-9-tetrahydrocannbinol