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Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
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Re: Department of Health and Human Services, Food and Drug Administration [Docket No. FDA-2018-N-1072]: International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; Cannabis Plant and Resin; Extracts and Tinctures of Cannabis; Delta-9-Tetrahydrocannabinol; Stereoisomers of Tetrahydrocannabinol; Cannabidiol; **Request for Comments** (FR Doc. 2018-07225).

Dear Dockets Management Staff:

On behalf of DrugWatch International, Inc., a 501c3 non-profit international organization incorporated in the state of IL and dedicated to the reduction of drug use disorders through education and prevention, the following public comment is offered in response to the request for comments cited above.

Background

The United States is party to several United Nations (UN) drug treaties, including the 1961 Single Convention on Narcotic Drugs, the 1971 Convention on Psychotropic Substances, and the 1988 Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances.

Cannabis and cannabis resin and extracts and tinctures of cannabis are listed in Schedule I of the 1961 Convention.¹ Tetrahydrocannabinol and a number of isomers and stereochemical variants are

¹ <http://undocs.org/ST/CND/1/Add.1/Rev.3>.

listed in Schedule I of the 1971 Convention.² The 1988 Convention did not address cannabis or its isomers and stereochemical variants.³

The designation, Schedule I, as used in UN conventions, differs from the designation of Schedule I, as used in the U.S. Controlled Substances Act (CSA, 21 USC § 801, *et seq.*). Under the CSA, Schedule I substances are not approved for medical use in the U.S.

In the 1971 UN Convention, Schedule I is reserved for “Substances whose liability to abuse constitutes an especially serious risk to public health and which have very limited, if any, therapeutic usefulness.”⁴ Besides cannabis and cannabis resin and extracts, tinctures of cannabis, and tetrahydrocannabinol (THC) and a number of its isomers and stereochemical variants, the UN’s Schedule I includes cocaine, diphenoxylate, fentanyl, hydrocodone, hydromorphone – substances that have therapeutic properties and are approved by member states, including the U.S., for medical use under strict supervision.

From this brief analysis, it would appear that treaty provisions regarding the international control of cannabis have been in place since at least the 1961 Convention, as amended by the 1972 Protocol. Of interest at this time because of its popularity and promise is **cannabidiol**, a phytocannabinoid derived from cannabis and described by the U.S. National Institutes of Health as “devoid of psychoactive activity, with analgesic, anti-inflammatory, antineoplastic and chemopreventive activities.”⁵

Cannabidiol (CBD) is not specifically listed in the schedules of the 1961, 1971, or 1988 UN drug conventions, yet it already has been approved as a medicine by several member states and is presently undergoing human clinical trials in the U.S.

At the 39th meeting of the WHO Expert Committee on Drug Dependence (ECDD) held in Geneva on November 6-10, 2017, a “Pre-Review Report” of CBD described the drug as follows:

“Cannabidiol (CBD) is one of the naturally occurring cannabinoids found in cannabis plants. It is a 21-carbon terpenophenolic compound which is formed following decarboxylation from a cannabidiolic acid precursor, although it can also be produced synthetically.

CBD can be converted to tetrahydrocannabinol (THC) under experimental conditions; however, this does not appear to occur to any significant effect in patients undergoing CBD treatment.

In experimental models of abuse liability, CBD appears to have little effect on conditioned place preference or intracranial self-stimulation. In an animal drug discrimination model

² <http://undocs.org/ST/CND/1/Add.2/Rev.3>.

³ <http://undocs.org/ST/CND/1/Add.3/Rev.2>.

⁴ http://www.unodc.org/documents/commissions/CND/CND_Sessions/CND_61/Scheduling_paper_short_8_March_final_FINAL.pdf.

⁵ <https://pubchem.ncbi.nlm.nih.gov/compound/cannabidiol#section=Top>.

CBD failed to substitute for THC. In humans, CBD exhibits no effects indicative of any abuse or dependence potential.

CBD has been demonstrated as an effective treatment of epilepsy in several clinical trials, with one pure CBD product (Epidiolex®) currently in Phase III trials. There is also preliminary evidence that CBD may be a useful treatment for a number of other medical conditions.

There is unsanctioned medical use of CBD based products with oils, supplements, gums, and high concentration extracts available online for the treatment of many ailments.

CBD is generally well tolerated with a good safety profile. Reported adverse effects may be as a result of drug-drug interactions between CBD and patients' existing medications.

Several countries have modified their national controls to accommodate CBD as a medicinal product.

To date, there is no evidence of recreational use of CBD or any public health related problems associated with the use of pure CBD."⁶

Discussion

Throughout recorded history, natural products derived from terrestrial and marine sources have been used for therapeutic purposes. It is estimated that less than 10 percent of the world's biodiversity has been evaluated for potential biological activity, meaning that many more beneficial compounds and chemicals likely are awaiting discovery.⁷

Whether CBD or any other active constituent in the cannabis plant has beneficial biological activity is a reasonable but not certain hypothesis. We believe that testing CBD for safety and efficacy in humans to treat conditions and diseases should proceed with strict adherence to clinical protocols designed and supervised by the Food and Drug Administration (FDA) as required by the federal Food, Drug, and Cosmetic Act (FDCA). While justification for using this approach should be self-evident for all drugs and biological substances, cannabinoid medications pose some unique challenges.

Since passage of the CSA in 1970, special interest groups advocating the legalization of cannabis have actively opposed any controls on the production, distribution, and use of cannabis. In the 1980s, in reaction to the AIDS-HIV problem, cannabis advocates took advantage of desperately ill patients to promote unapproved medical uses for smoked marijuana. As a hallucinogen and intoxicant, many who smoked cannabis to relieve the symptoms of this once-deadly disease spoke of it as a miracle drug. Proponents of medicinal cannabis ignored conventional means for investigating the safety and

⁶ http://www.who.int/medicines/access/controlled-substances/5.2_CBD.pdf.

⁷ Dias DA, Urban S, Roessner U. A Historical Overview of Natural Products in Drug Discovery. *Metabolites*. 2012;2(2):303-336.

efficacy of the drug via the IND-NDA⁸ process and, instead, used the political route to approve what they called *medical marijuana*.

Having the benefit of several decades of data to weigh the risks and benefits of smoked marijuana, the evidence indicates that the health risks far outweigh whatever perceived benefits users of marijuana report. In this regard, I would commend to you the detailed and robust studies reported by Dr. Stuart Reece of the University of Western Australia, School of Psychiatry and Clinical Neurosciences, Perth, Australia. Dr. Reece, a member of DrugWatch International, has submitted public comments to this docket (Comment Tracking No. 1k2-9217-gpvj) describing in detail cannabis-related arteriopathy and teratogenicity.

Dr. Reece has studied an increase in major birth defects in Colorado that appears to correlate closely with the expanded use of cannabis in that state. Using published data, Dr. Reece found that:

“Over the period 2000-2013 Colorado almost doubled its already high congenital anomaly rate rising from 4,830 anomalies/65,429 births (7.4%) to 8,165/65,004 (12.6%); the US mean is 3.1%. Major cardiovascular defects rose 61% (number and rate); microcephaly rose 96% (from 30 to 60 cases peaking at 72 in 2009); and chromosomal anomalies rose 28% (from 175 to 225, peaking at 264 in 2010). Over the whole period this totals to 87,772 major congenital anomalies from 949,317 live births (9.25%).

The use of cannabis in Colorado can be determined from the SAMHSA National Survey on Drug Use and Health. A close correlation is noted between major congenital anomaly rates and rates of cannabis use in Coloradans >12 years ($R=0.8825$; $P=0.000029$). Although data is not strictly comparable across U.S. registries, the Colorado registry is a passive rather than active case-finding registry and so might be expected to underestimate anomaly rates. Given the Colorado birth rate remained almost constant over the period 2000-2013, rising only 3.6%, a simple way to quantitate historical trends is to simply project forwards the historical anomaly rate and compare it to the rise in birth numbers. However rather than remaining relatively stable in line with population births, selected defects have risen several times more than the birth rate.

Colorado had an average of 67,808 births over the period 2000-2013 and experienced a total of 87,772 birth defects, 20,152 more than would have been predicted using 2000 rates. Given the association between cannabis use and birth defects and the plausible biological mechanisms, cannabis may be a major factor contributing to birth congenital morbidity in Colorado. If we accept this and apply the ‘Colorado effect’ to the over 3,945,875 births in USA in 2016 we calculate an excess of 83,762 major congenital anomalies annually nationwide if cannabis use rises in the US to the level that it was in Colorado in 2013.

In reality both cannabis use and cannabis concentration is rising across USA following legalization which further implies that the above calculations represent significant

⁸ IND = Investigational New Drug; NDA = New Drug Application. The sequence of obtaining approval of these applications by the FDA is required for developing and marketing new drugs.

underestimations 159,160. This CRCSN data series terminates in 2013 prior to full legalization in 2014. Moreover, parents of children harbouring severe anomalies may frequently elect for termination, which will again underestimate numbers of abnormal live births.

In California 7% of all pregnant mothers were recently shown to test positive for cannabis exposure, including almost 25% of teenage mothers in 2015 so cannabinoids clearly constitute a significant population-wide teratological exposure. This is particularly relevant to cannabis genotoxicity as many studies show a dramatic up-tick in genotoxic effect in the dose-response curve for both tetrahydrocannabinol and cannabidiol above a certain threshold dose as higher, sedating levels are reached. Cannabis is usually used amongst humans for its sedative effects.

Other examples of high congenital anomaly rates accompanying increased cannabis use include North Carolina, Mexico, Northern Canada, New Zealand and the Nimbin area in Australia.”⁹

These truly are startling numbers and brings to mind the global health crisis that followed the introduction of thalidomide in the late 1950s. Like cannabis, thalidomide was popular in a generation that often appeared oblivious to the risks of taking tranquilizers and sedatives to deal with common ailments. Thalidomide was approved as an over-the-counter drug in Germany in 1957. By demanding additional safety studies, the FDA protected Americans from the brunt of the thalidomide tragedy. It must do the same today on the questions raised by Dr. Reece and others with respect to investigating the link between cannabis use and congenital birth defects.

With respect to CBD, while this molecule in the cannabis plant lacks psychoactivity and, therefore, has little or no potential for abuse, it may be used as a strawman to promote the legalization of other forms of cannabis as a medicine. The Internet has many sellers of CBD products promoting medicinal uses of the drug and in the process asserting false medical claims in violation of the law. A simple Google search using the search terms, “CBD sellers,” returned 3,970,000 results in 0.44 seconds. In November 2017, the FDA issued warning letters to four such companies alleging that they were making false medical claims for their CBD products.¹⁰

While the FDA’s action is laudatory, it is far too little and far too late, given the enormous size and momentum of this online activity. In addition, bona fide cannabinoid researchers investigating the medicinal properties of CBD report that their work is complicated by the proliferation of Internet dealers selling contaminated CBD products or products fraudulently claiming to contain CBD.

In 2016, a research letter submitted to JAMA described how investigators purchased via the Internet 84 products that purported to contain CBD. After using high performance liquid chromatography to analyze the contents of the products, they found that 36 samples were underlabeled in CBD content,

⁹ Public comment, dated April 22, 2018, by Dr. Stuart Reece, Associate Professor, University of Western Australia, submitted to FDA Dockets Staff re: Docket No. FDA-2018-N-1072 [Internal references, figures and charts cited in original comment omitted in above-quoted reference].

¹⁰ <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm583295.htm>.

22 samples were overlabeled, and 26 samples were accurately labeled. THC was detected in 18 of the 84 samples.¹¹

Requiring sponsors of CBD products to satisfy the safety and efficacy standards of the FDA's IND-NDA process would likely reduce the availability of inaccurately labeled and/or contaminated CBD products.¹² Some CBD researchers have reported that any amount of THC present in a CBD medication is a form of contamination that can reduce or destroy whatever therapeutic effects that pure CBD may have.

Moreover, we believe that the ECDD's "Pre-Review Report" on CBD issued in 2017 is ambiguous in stating that, "To date, there is no evidence of recreational use of CBD or any public health related problems associated with the use of pure CBD." While this may be true with respect to "pure" CBD, there is evidence that unregulated CBD sold via the Internet is not always pure or correctly labeled as to dosage strength. As mentioned above, in a small sample assay of 84 CBD products purchased online, 18 (21%) were found to contain THC along with the CBD and only about a third (31%) were found to be accurately labeled.¹³

DrugWatch International recommends that the above analysis be furnished to the ECDD as part of its medical and scientific evaluation of CBD. At a minimum, WHO should schedule CBD in a category that appropriately ensures its integrity as a manufactured pharmaceutical product, dispensed by prescription-only, and subjected to other quality controls that protect the health of its users.

With respect to control issues pertaining to the other four substances forming the subject matter of the upcoming ECDD meeting, DrugWatch International recommends that the FDA provide to the ECDD the full medical and scientific evaluation that the FDA authored in 2015 as part of the evaluation process involving a citizen's petition for rescheduling cannabis submitted to the Drug Enforcement Administration (DEA).¹⁴

Criteria used by the WHO in making drug scheduling decisions are very similar to those used by the DHHS (i.e., FDA) and the DEA in scheduling drugs and other substances under the CSA. In 2011, the DEA received a citizen's petition asking for the initiation of rulemaking proceedings under the rescheduling provisions of the CSA "to have marijuana and 'related items' removed from Schedule I

¹¹ Bonn-Miller MO, Loflin MJE, Thomas BF, Marcu JP, Hyke T, Vandrey R. Labeling Accuracy of Cannabidiol Extracts Sold Online. *JAMA*. 2017;318(17):1708-1709.

¹² It is to be noted that DrugWatch International, Inc., has filed a citizen's petition with the FDA asking that rulemaking procedures be initiated to establish a "negative monograph" for cannabis and cannabinoid medications and proposed medications (including CBD). The FDA has already established 22 negative monographs to cover OTC products for thumb sucking, nailbiting, and hair loss. Products asserting claims for these indications must go through the FDA's IND-NDA process. The DrugWatch petition asks that cannabis-based medications be required to satisfy the same requirement. See: Docket ID: FDA-2017-P-6692-0001; available at: <https://www.regulations.gov/document?D=FDA-2017-P-6692-0001>.

¹³ Bonn-Miller MO, Loflin MJE, Thomas BF, Marcu JP, Hyke T, Vandrey R. Labeling Accuracy of Cannabidiol Extracts Sold Online. *JAMA*. 2017;318(17):1708-1709.

¹⁴ <https://www.gpo.gov/fdsys/pkg/FR-2016-08-12/pdf/2016-17954.pdf>.

of the CSA and rescheduled as medical cannabis in Schedule II.”¹⁵ Under the CSA, before DEA can initiate a change in drug scheduling, it must request from the Secretary of Health and Human Services a medical and scientific evaluation and recommendation.¹⁶

On June 25, 2015, Karen B. DeSalvo, MD, MPH, MSc, Assistant Secretary of Health responded to the DEA acting administrator with a detailed medical and scientific evaluation of marijuana prepared by the FDA and the National Institute on Drug Abuse (NIDA). The letter contained a recommendation to maintain marijuana in Schedule I of the CSA.¹⁷ The medical and scientific evaluation assessed eight factors identified in the CSA:

- (1) Its actual or relative potential for abuse;
- (2) Scientific evidence of its pharmacological effect, if known;
- (3) The state of current scientific knowledge regarding the drug or other substance;
- (4) Its history and current pattern of abuse;
- (5) The scope, duration, and significance of abuse;
- (6) What, if any, risk there is to the public health;
- (7) Its psychic or physiological dependence liability;
- (8) Whether the substance is an immediate precursor of a substance already controlled under this subchapter.¹⁸

Based on the medical and scientific evaluation of cannabis and the Assistant Secretary’s recommendation to the DEA acting administrator to maintain marijuana in Schedule I, the citizen’s petition for rescheduling marijuana was denied. As previously stated, the eight-factor medical and scientific evaluation performed by FDA addresses criteria similar to criteria used by the ECDD and WHO in scheduling drugs covered by UN conventions. For this reason and because these comments are intended to assist the DHHS and FDA in responding to the WHO’s request for assistance, we are quoting below the complete medical and scientific evaluation of marijuana and the recommendation that was provided to DEA on June 25, 2015 by the Assistant Secretary and published in the Federal Register on August 12, 2016.¹⁹

Medical and Scientific Evaluation of Marijuana

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:

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

¹⁵ *Ibid.*

¹⁶ 21 USC § 811(b).

¹⁷ <https://www.gpo.gov/fdsys/pkg/FR-2016-08-12/pdf/2016-17954.pdf>.

¹⁸ 21 USC § 811(c).

¹⁹ <https://www.gpo.gov/fdsys/pkg/FR-2016-08-12/pdf/2016-17954.pdf>.

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 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 population 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 of 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 a 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 month 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 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 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 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 investigation supplies is likely because of the widespread availability of illicit marijuana of equal or greater amounts of delta9-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 publicly 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 delta9-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 most current research literature on cannabinoids.

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 delta9-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, CB1 and CB2, 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, CB1 and CB2, 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 (Gi), 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, alpha2-adrenoreceptors, dopamine (D2), and serotonin (5-HT1).

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).

CB1 receptors are found primarily in the central nervous system but are also present in peripheral tissues. CB1 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, CB1 receptors are found in the immune system and numerous other peripheral tissues (Petrocellis and Di Marzo, 2009). However, the concentration of CB1 receptors is considerably lower in peripheral tissues than in the central nervous system (Herkenharn et al., 1990 and 1992).

CB2 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, CB2 receptors are found predominantly in B lymphocytes and natural killer cells (Bouaboula et al., 1993). CB2 receptors may mediate cannabinoids’ immunological effects (Galiegue et al., 1995). Additionally, CB2 receptors have been localized in the brain, primarily in the cerebellum and hippocampus (Gong et al., 2006). The distribution of CB2 receptors throughout the body is less extensive than the distribution of CB1 receptors (Petrocellis and Di Marzo, 2009). However, both CB1 and CB2 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.

Delta9-THC and cannabidiol (CBD) are two abundant cannabinoids present in marijuana. Marijuana’s major psychoactive cannabinoid is delta9-THC (Wachtel et al., 2002). In 1964,

Gaoni and Mechoularn first described delta9-THC's structure and function. In 1963, Mechoularn and Shvo first described CBD's structure. The pharmacological actions of CBD have not been fully studied in humans.

Delta9-THC and CBD have varying affinity and effects at the cannabinoid receptors. Delta9-THC displays similar affinity for CB1 and CB2 receptors but behaves as a weak agonist for CB2 receptors. The identification of synthetic cannabinoid ligands that selectively bind to CB2 receptors but do not have the typical delta9-THC-like psychoactive properties suggests that the activation of CB1-receptors mediates cannabinoids' psychotropic effects (Hanus et al., 1999). CBD has low affinity for both CB1 and CB2 receptors (Mechoulam et al., 2007). According to Mechoulam et al. (2007), CBD has antagonistic effects at CB1 receptors and some inverse agonistic properties at CB2 receptors. When cannabinoids are given subacutely to rats, CB1 receptors down-regulate and the binding of the second messenger system coupled to CB1 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 delta9-THC, in animal models. However, self-administration of delta9-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 delta9-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 delta9-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 CB1 cannabinoid receptor agonist-antagonist, can block this rewarding effect. Other studies show that naïve squirrel monkeys can be successfully trained to self-administer delta9-THC intravenously (Justinova et al., 2003). The maximal responding rate is 4 mg/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 delta9-THC (Justinova et al., 2004).

Additionally, data demonstrate that under specific conditions, rodents self-administer cannabinoids. Rats will self-administer delta9-THC when applied intracerebroventricularly (i.c.v.), but only at the lowest doses tested (0.01–0.02 mg/infusion) (Braida et al., 2004). SR141716 and the opioid antagonist naloxone can antagonize this effect. However, most studies involve rodents self-administering the synthetic cannabinoid WIN 55212, a CB1 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 delta9-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 delta9-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 m-opioid receptors do not develop CPP to delta9- 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 delta9- THC, 11-hydroxy-delta9-THC, also generalizes (following oral administration) to the stimulus cues elicited by delta9-THC (Browne and Weissman, 1981). Twenty-two other cannabinoids found in marijuana also fully substitute for delta9-THC. However, CBD does not substitute for delta9-THC in rats (Vann et al., 2008).

Discriminative stimulus effects of delta9-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 delta9-THC.

Central Nervous System Effects Human Physiological and Psychological 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 delta9-THC) over lower concentrations (0.63 percent delta9-THC) (Chait and Burke, 1994). Nonetheless, frequent marijuana users (>100 times of use) were able to identify a drug effect from low-dose delta9-THC better than occasional users (<10 times of use) while also experiencing fewer sedative effects from marijuana (Kirk and de Wit, 1999).

The petitioners contend that many of marijuana's naturally occurring cannabinoids mitigate the psychoactive effects of delta9-THC, and therefore that marijuana lacks sufficient abuse

potential to warrant Schedule I placement, because Marinol, which is in Schedule III, contains only delta9-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 [(–)- delta9-(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 delta9-THC by smoking is 2.6 to 3 times more potent than delta9- 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 delta9-THC from marijuana (0.1–9.5 percent delta9- THC range) or hashish (10–30 percent delta9-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 delta9-THC, only three of the cannabinoids present in marijuana were simultaneously administered with delta9-THC to examine how the combinations of these cannabinoids such as CBD, cannabichromene (CBC) and cannabinol (CBN) influence delta9-THC's psychoactive effects. Dalton et al. (1976) observed that smoked administration of placebo marijuana cigarettes containing injections of 0.15 mg/kg CBD combined with 0.025mg/kg of delta9-THC, in a 7:1 ratio of CBD to delta9-THC, significantly decreased ratings of acute subjective effects and "high" when compared to smoking delta9-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 delta9-THC concentration by weight. For each strength of delta9-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 delta9-THC marijuana cigarettes, with administrations consisting of either low CBC

(between 0.1–0.2 percent CBD concentration by weight) and low CBD (between 0.1–0.4 percent CBD concentration by weight), high CBD (>0.5 percent CBD concentration by weight) and low CBD, or low CBD 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 delta9-THC dissolved in liquid (in a ratio of at least 1:2 CBD to delta9-THC) reduced the subjective effects produced by delta9-THC alone (Karniol et al., 1974). Additionally, orally administering a liquid mixture combining 1 mg/kg CBD with 0.5 mg/kg of delta9-THC (ratio of 2:1 CBD to delta9-THC) decreased scores of anxiety and marijuana drug effect on the Addiction Research Center Inventory (ARCI) compared to delta9-THC alone (Zuardi et al., 1982). Lastly, oral administration of either 12.5, 25, or 50 mg CBN combined with 25 mg delta9-THC dissolved in liquid (ratio of at least 1:2 CBN to delta9-THC) significantly increased subjective ratings of “drugged,” “drowsy,” “dizzy,” and “drunk,” compared to delta9-THC alone (Karniol et al., 1975).

Even though some studies suggest that CBD may decrease some of delta9-THC’s psychoactive effects, the ratios of CBD to delta9-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 delta9-THC naturally present in marijuana plant material and they found out that varying the amount of CBD actually had no effect on delta9-THC’s psychoactive effects (Ilan et al., 2005). Because most marijuana currently available on the street has high amounts of delta9-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 delta9-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 delta9-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 mg/kg and 500 mg/kg of delta9-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 mg/kg delta9-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 delta9-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 delta9-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 delta9-THC. However, Fant et al. (1998) showed that the morning after exposure to 1.8 percent or 3.6 percent smoked delta9-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.”⁷ 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 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” (Maremmanni 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-Lending 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 delta9- THC produce tachycardia and may increase blood pressure (Capriotti et al., 1988; Benowitz and Jones, 1975). Some evidence associates the tachycardia produced by delta9-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 delta9-THC ingestion produces bradycardia and hypotension (Benowitz and Jones, 1975). Plant-derived cannabinoids and endocannabinoids elicit hypotension and bradycardia via activation of peripherally-located CB1 receptors (Wagner et al., 1998). Specifically, the mechanism of this effect is through presynaptic CB1 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 delta9-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 delta9-THC (18 mg/marijuana cigarette) or oral delta9-THC (10 mg three times per day for 3 days and on the morning of the fourth day) showed no changes in plasma adrenocorticotrophic 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, delta9-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 delta9-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 delta9-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 CB1/CB2 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 delta9-THC, an oral tablet containing delta9-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 delta9-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 delta9-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* (*Humbraculigerum*) accumulates these compounds (Appendino et al. 2011).

Among the cannabinoids found in marijuana, delta9-THC (alternate name delta1-THC) and delta-8- tetrahydrocannabinol (delta8-THC, alternate name delta6-THC) produce marijuana's characteristic psychoactive effects. Because delta9-THC is more abundant than delta8-THC, marijuana's psychoactivity is largely attributed to the former. Only a few varieties of marijuana analyzed contain delta8-THC at significant amounts (Hively et al., 1966). Delta9-THC is an optically active resinous substance, insoluble in

water, and extremely lipid soluble. Chemically, delta9-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 delta9-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 delta9-THC, is also a minor naturally-occurring cannabinoid with weak psychoactivity. Chemically, CBN is 6,6,9-trimethyl-3-pentylbenzo[c]chromen-1-ol.

Different marijuana samples derived from various cultivated strains may differ in chemical constituents including delta9-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 delta9-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 delta9-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 saliva 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 delta9-THC averages over 12 percent by weight. However, specially grown and selected marijuana can contain 15 percent or greater delta9-THC (Appendino et al., 2011). Thus, a 1-gram marijuana cigarette might contain delta9-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 delta9-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 delta9-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,⁸ 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,

The absorption, metabolism, and pharmacokinetic profile of delta9-THC, cannabinoids, and drug products containing delta9-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 delta9-THC and other cannabinoids from smoked marijuana is difficult because a subject's smoking behavior during an experiment varies (Agurell et

al., 1986; Heming et al., 1986; Huestis et al., 1992a). Each puff delivers a discrete dose of delta9- 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 delta9-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 delta9-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). Delta9-THC is delivered to the brain rapidly and efficiently as expected of a very lipid soluble drug.

The bioavailability of the delta9-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 delta9-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 (Heming et al., 1986; Johansson et al., 1989). After smoking, delta9-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 delta9- 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 delta9-THC doses compared to smoking marijuana. Oral bioavailability of delta9-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 delta9-THC, delta9-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 delta9-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. Delta9-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 delta9-THC following oral ingestion is 11-hydroxy-delta9-THC. This metabolite is approximately equipotent to delta9-THC in producing marijuana-like subjective effects (Agurell et al., 1986, Lemberger and Rubin, 1975). After oral administration, metabolite levels may exceed that of delta9-THC and thus contribute greatly to the pharmacological effects of oral delta9-THC or marijuana.

Plasma clearance of delta9-THC approximates hepatic blood flow at about 950 ml/min or greater. The rapid disappearance of delta9-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 delta9-THC and other cannabinoids from tissues and subsequent metabolism results in a long elimination half-life. The terminal half-life of delta9-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 delta9-THC to range from 23 to 28 hours in heavy marijuana users to 60 to 70 hours in naive users. In addition to 11-hydroxy-delta9-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 delta9-THC dose is eliminated in feces, and about 33 percent in urine. Delta9-THC enters enterohepatic circulation and undergoes hydroxylation and oxidation to 11-nor-9-carboxy-delta9-THC. The glucuronide is excreted as the major urine metabolite along with about 18 non-conjugated metabolites. Frequent and infrequent marijuana users metabolize delta9-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 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 “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:10

- 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 G) of the Food, Drug and Cosmetic Act, 21 U.S.C. 321G), 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.”

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 delta9-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."¹¹

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 PubMed¹² 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 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)

According to 2012 NSDUH14 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 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.¹⁵ 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.¹⁶ 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)

According to MTF, 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 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.

Drug Abuse Warning Network (DAWN)

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, DAWN20 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.

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)

Primary marijuana abuse accounted for 18.1 percent of all 2011 TEDS22 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.

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.²³

TEDS data for 2011 show that 18.1 percent of all admissions were for primary marijuana abuse.²⁴ 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.

The following states how the DSM-V (2013) of the American Psychiatric Association describes the consequences of Cannabis²⁵ 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 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 8th, 10th, and 12th 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 delta9-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 P10026 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.

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.

[**Note:** some internal references and citations are omitted, as is Table 1 showing trends in drug use from the Monitoring the Future Survey. These items are available in the Federal Register copy at: <https://www.gpo.gov/fdsys/pkg/FR-2016-08-12/pdf/2016-17954.pdf>]

The above medical and scientific evaluation of marijuana prepared by the FDA and NIDA is a timely and comprehensive analysis of why marijuana must remain a Schedule I controlled substance in the U.S. It should be shared with the WHO at the upcoming ECDD meeting in June. For more than a century, the U.S. has worked with the international community to reduce the abuse and misuse of drugs. The humanitarian ideal of a safe and healthy world free from the debilitating effects of drug abuse transcends political and parochial concerns. As technology changes the world and blurs our natural boundaries it becomes even more important that we work together to protect global public health.

Today, it is possible via the Internet for someone in Country A to communicate with someone in Country B who agrees to sell the person in Country A prohibited drugs that are produced in Country C. The shipment may be transported via Countries D and E before they are received by the customer in Country A. Payment may be made anonymously via the Internet to a bank account in Country F that has no knowledge of the underlying transaction. In all, a half-dozen or more countries may be involved in this one simple transaction - something that may occur thousands of times a day all over

the world wherever there's someone with a computer or a smart phone. Presently and for the foreseeable future, the only effective remedy we have for protecting our vulnerable populations against this type of crime is to share information and harmonize controls via international conventions such as those described herein.

The UN's *World Drug Report* for 2017 estimates that 29.5 million persons in the world suffer from substance use disorders. As a frame of reference, this estimate is more than the combined populations (2017) of Portugal, Laos, and Greece. The UN and the League of Nations, its predecessor, have protected the world's public health for almost a century by providing, among other things, a forum and a process for establishing international agreements to control the illicit traffic in drugs of abuse. From the very first days of the League's Opium Commission, the organizing principle has been to restrict access to controlled substances for medical and scientific purposes only. Today, more than ever, this principle should guide the WHO in regulating the production and commerce of CBD and other active constituents of cannabis.

In the opening paragraphs of this public comment we discussed the status of CBD and offered that control mechanisms employed by the international community should follow the practice of the FDA in requiring clinical trials and protocols to establish appropriate pharmaceutical standards for purity and dosage strength and for ensuring the safety and efficacy of CBD for treating approved indications. The proliferation of online CBD dealers operating beyond the jurisdiction of desperate patients attracted by false medical claims and tricked into buying bogus, mislabeled and/or contaminated CBD, necessitates close cooperation among all member states if this cruel trade is to be halted.

On the question of CBD, we wish to note that the ECDD's "Pre-Review Report" of CBD published after its November 2017 meeting and in which it stated, "CBD is generally well tolerated with a good safety profile" may be premature and unwarranted. As mentioned earlier, there are serious questions about the genotoxicity of cannabis, especially with respect to associating its use with rates of congenital birth defects. Whether and to what extent CBD contributes to genotoxicity is worth taking the time to find out before declaring it *safe* because its current users tolerate it well.

The study of CBD as a therapeutic agent is relatively new. An online search of the National Library of Medicine ("PubMed") using the search term "cannabidiol" returned 818 responses of which 637 (78%) were published after 2000. This alone should cause regulatory bodies such as the FDA and the WHO to move cautiously in permitting open access to a drug whose unknown but potentially serious side effects may be hidden for generations to come. Moreover, extra caution is warranted in the evaluation and control of *any* cannabinoid medicine, given the influence of special interests to commercialize and develop a global cannabis industry. Fortunately, when it comes to international drug control, the UN has always placed the economic and political interests of member states secondary to the health and welfare of their people.

Although the U.S. was not the first nation to amend its marijuana policies to conform with political rather than medical and scientific standards, this fact, alone, should not diminish efforts by the UN and other world bodies to reestablish evidence-based standards for developing and distributing medicinal controlled substances. These standards have benefitted the U.S. and the world for many decades. They were developed and strengthened in response to the previously mentioned thalidomide tragedy that occurred more than a half century ago. Today, a growing body of scientific evidence suggests that the increased use of cannabis, especially in certain forms, may be associated with

increases in congenital birth defects. To those who remember all too well the missteps of the past with respect to thalidomide, these warnings about cannabis are all too familiar and alarming.

Fortunately, today's technology to evaluate proposed medicines to identify dangerous side effects before they are approved and made available to the public gives us peace of mind and a way to safeguard patients from potentially toxic and dangerous medicines. But these systems are effective for this purpose only if they are employed. When, as in the case of medical marijuana, they are bypassed in favor of the political process, these elegant systems are worthless. By using the political process as an expedient substitute for evidence-based clinical standards, we risk exposing millions of people to potentially catastrophic effects that, as in the case of thalidomide, may not be evident until future generations are forced to pay a horrible and deadly price for our missteps.

Sincerely,

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