BENJAMIN B. WAGNER
United States Attorney
RICHARD BENDER
SAMUEL WONG
GREGORY T. BRODERICK
Assistant United States Attorneys
501 I Street, Suite 10-100
Sacramento, CA 95814
Telephone: (916) 554-2991
Facsimile: (916) 554-2900

Attorneys for Plaintiff
United States of America

IN THE UNITED STATES DISTRICT COURT

EASTERN DISTRICT OF CALIFORNIA

UNITED STATES OF AMERICA Plaintiff, v. BRIAN SCHWEDER, et. al. Defendant,	CASE NO. 2:11-CR-00449-KJM-16 **DECLARATION OF BERTHA MADRAS, PH.D**

I, Bertha K. Madras, Ph.D, declare as follows:

1. I am a Professor of Psychobiology at Harvard Medical School, Department of Psychiatry. My office is located in the Alcohol and Drug Abuse Program at McLean Hospital, an affiliate hospital of Harvard. I have been retained to offer opinions in *United States v. Schweder, et. al.*, Case No. 2:11-CR-0449-KJM (E.D. Cal.). I am not employed by the Department of Justice, the Drug Enforcement Administration (DEA), or any other federal office or agency. I neither speak for, nor set policy for, these agencies. Nor can I speculate about, or predict the outcome of, the rescheduling petition currently pending before DEA. Rather, my opinions are my own, are based in science, and reflect my 50 years of education, research, and experience in the relevant area.

I. SUMMARY OF QUALIFICATIONS

2. I have dedicated a significant portion of my career to researching and working in the areas of abuse and addiction. During my career, I have engaged in significant study of how psychoactive and therapeutic drugs affect the brain (including cocaine, ecstasy or MDMA,

methamphetamine, marijuana's active constituent THC, other cannabinoids, anti-psychotic, anti-epileptic, anti-hyperactivity, and anti-narcoleptic drugs) and in development of medications and brain imaging probes. My recent research focuses on contrasting molecular and behavioral effects of THC and psychostimulant drugs on adolescent and adult brain. A brain imaging drug I invented with collaborators was evaluated through the FDA process. I am familiar with the literature showing marijuana's effects, the potential (or lack thereof) of isolated cannabinoids as medicine, and the adverse effects of marijuana use. I submit this declaration as my direct testimony on the rationality of marijuana's "continued inclusion" as a Schedule I Controlled Substance.

3. I graduated with honors from McGill University in 1963, earning a Bachelor's of Science in Honours Biochemistry. As a J.B. Collip Fellow of the Faculty of Medicine, I was awarded a Doctor of Philosophy in Biochemistry (metabolism and pharmacology, including hallucinogens such as LSD, psilocybin) from McGill University in 1967. Following my Ph.D, I completed two post-doctoral fellowships from 1967-69. The first was in the Department of Biochemistry at Tufts University, continued in the Department of Biochemistry at Cornell University Medical College when my mentor relocated as Chair of Biochemistry at Cornell University Medical College mid-training. During this period, I laid the groundwork for future development of a widely used anti-cancer (lymphoblastic leukemia) drug, asparaginase. My other post-doctoral fellowship was in the Department of Biology at the Massachusetts Institute of Technology. Thereafter, I was appointed Research Associate at the Massachusetts Institute of Technology from 1972-1974, and an Assistant Professor in the Departments of Pharmacology and Psychiatry at the University of Toronto. In 1986, I was appointed Assistant Professor at Harvard Medical School. Subsequently, I was promoted to Associate Professor and then to the rank of Professor, with a cross-appointment to the Department of Psychiatry, the Massachusetts General Hospital. I also founded and chaired the Division of Neurochemistry at Harvard Medical School's New England Primate Research Center, a multidisciplinary, translational research program which spanned chemical design, molecular and cellular biology, behavioral biology, and brain imaging approaches.

4. As an educator, I developed and served as Course Director of the Advanced Biomedical Sciences: Substance abuse and addictive processes since 1991, a course on addictions offered to fourth year medical students at Harvard Medical School. I was a founding member of Harvard Medical

School's Division on Addictions and served as Associate Director for Public Education from 1998-2006 at Harvard Medical School's Division on Addictions. I have delivered numerous Continuing Medical Education Courses on the Biology of Addiction, with a recent emphasis on marijuana. In 2001, I founded, directed, and delivered lectures in an international Cold Spring Harbor Course on the Cell Biology of Addiction, which included a section on marijuana.

5. I have served on a number of academic and medical committees. At Harvard Medical School, I was a member of the Subcommittee of Professors, which recommends promotions and appointments to the rank of full Professor. I was also a member of the Department of Psychiatry's Research Committee, and the Steering Committee for the Division on Addictions. Prior to Harvard, I founded and chaired the University of Toronto, Faculty of Medicine's Neuroscience course and program committee. Additionally, from 1980-82, I served on both the Research and Educational Advisory Committees at the Clarke Institute of Psychiatry and was Chair of the Ontario Mental Health Foundation (Ontario Ministry of Health), Fellowships and Awards Committee (1988-1990). Through the course of my career, I have been asked to serve on more than 50 National Institutes of Health (NIH) committees and other government and private sector advisory boards, a reflection of my expertise in neurobiology, brain imaging, addictions, analysis of study design, and the validity of scientific data. These include the National Institute on Drug Abuse (NIDA) Medications Development Scientific Advisory Board, the NIDA Council work group on mechanisms of transferring NIDA-sponsored addiction treatment research to community treatment centers, numerous grant review panels for NIDA and other NIH institutes, Advisory Board of the Addiction Studies Institute for Journalists, the Science and Technology Advisory Committee of Brookhaven National Laboratory. I also served on the Special Review Committee for the Office of National Drug Control Policy and the U.S. Department of Education's Safe and Drug-free School Advisory Committee (2007-2008).

6. In addition to my academic and professional work, I have served in public policy positions. In 2005, I was nominated by the President of the United States to be the Deputy Director for Demand Reduction (prevention, intervention, treatment) for the White House Office of National Drug Control Policy ("ONDCP"). My nomination was confirmed by the United States Senate with unanimous consent, and I served in that capacity until fall of 2008. Among other initiatives, I

spearheaded expansion of alcohol and drug screening, brief intervention and referral to treatment (SBIRT) services, and led the successful effort to obtain Medicare, Medicaid, and CPT billing codes to reimburse for these services. I also generated the first publication of official SBIRT effectiveness data, gleaned from more than 450,000 subjects.

7. I am a member of numerous professional societies: American College of Neuropsychopharmacology (1994-present), DANA Alliance for Brain Initiatives (1994-present), College on Problems of Drug Dependence (1989-present), and the Society for Neuroscience (1987-2014). I also served on committees for these professional societies: Public Information Committee, Society for Neuroscience, 1992-95; College on Problems of Drug Dependence (Board member; Membership Committee, 1994-2001; Media Committee, 1994-97 & 2009-present, Chair 2013-present); Bowman Grey School of Medicine, External Advisory Board for the Center for the Neurobiological Investigation of Drug Abuse (1998-2006).

8. In a continuing effort to translate scientific discoveries for the public good, I have given more than 100 public lectures on the science of addiction, including more than 30 recent presentations on the subject of marijuana. I have also distributed an array of slide presentations on marijuana and written summaries of marijuana science, upon request. I testified twice in sessions of the Maryland Legislature on medical marijuana bills in 2008. In 1998, I presented at a NIDA Town Meeting on the neuroscience of drug abuse and addiction. In 2000 and in 2009, I spoke in South Africa on shaping drug policy to emerging scientific data, have delivered a number of drug policy presentations to the Organization of American States, and other government agencies internationally. My audiences have included judges, lawyers, policy-makers, legislators, law enforcement agents, educators, parents, and high school students, both in the United States and on four other continents. I have spoken at the Department of Public Health and Massachusetts Judicial Institute on "The science of substance abuse and the brain." Recently, in 2011, I presented the case against medical marijuana to the Albany State Governor's Office on medical marijuana. I directed a NIDA-sponsored exhibit titled "Changing your Mind: Drugs in the Brain," at the Museum of Science in Boston (1994-2006), which included a CD (licensed by Disney in 2006), and a play, and was a major contributor to the story board of a joint NIDA/DEA-sponsored exhibit in Times Square, New York.

9. I have published more than 140 scientific articles and book chapters in my area of research. Several are specific to marijuana, including studies of cannabinoid and dopamine receptor agonists and their synergistic sedative effects in nonhuman primates, and cannabinoid receptor agonist and antagonist effects on motor function in a nonhuman primate model of Parkinson's disease. My most recent preclinical research, presented at 2013 and 2014 annual meetings, documents the effects of THC, the main psychoactive constituent of marijuana, on genes in the adolescent brain implicated in brain development. I am also the co-editor of a number of scientific textbooks, including "Imaging of the Human Brain in Health and Disease (2013)," with a chapter on imaging marijuana signaling systems in human brain. I am the principal editor of "The Cell Biology of Addiction," and principal editor of a book on the impact of drug abuse on the brain, titled "The Effects of Drug Abuse on the Human Nervous System," which includes two comprehensive chapters on marijuana (2013). I hold 19 patents, for novel medications, and for a class of agents that image dopamine brain cells affected by addictive drugs. This invention was recently highlighted in the Better World Report as one of 25 technology transfer innovations that changed the world.

10. I am honored to be the recipient of the Marion W. Fischman lectureship award by the College on Problems of Drug Dependence for "outstanding woman scientist in drug abuse research," the Founders Award of the American Association of Addiction Psychiatry, a NIDA Public Service Award, a MERIT award from NIDA-NIH, and others.

11. Further information, including research grants I have been awarded, as well as other research, academic duties and a bibliography of my significant publications (including peer-reviewed scientific publications (142), book chapters, reviews/editorials (22), published books/monographs (4), and numerous others), are listed in my Curriculum Vitae, attached hereto as Exhibit A. My most recent commentary, for the Proceedings of the National Academy of Science, 2014, in press, is titled "Dopamine Challenge Reveals Neuroadaptive Changes in Marijuana Abusers." A non-exhaustive bibliography of materials I considered is attached hereto as Exhibit B.

II. SUMMARY OF OPINIONS

12. "Marihuana" was listed as a Schedule I Controlled Substance with the adoption of the original Controlled Substances Act in the 1970s. Although the Controlled Substances Act gives the Attorney General

the authority to reschedule or de-schedule controlled substances, the Attorney General has delegated this authority to DEA, which periodically works with the Food and Drug Administration ("FDA") and NIDA in determining whether to amend the Controlled Substance schedules. Despite several petitions over the past 40 years, neither DEA, the Attorney General, nor the Congress have decided to alter marijuana's placement on Schedule I. It is my understanding that this Court has ordered a hearing "to probe the scientific and medical information" regarding "the continued inclusion of marijuana as a Schedule I controlled substance." For the reasons set forth below, it is my opinion that the current classification of marijuana on Schedule I is strongly supported by valid scientific research and medical evidence.

13. As set forth in 21 U.S.C. § 812(b)(1), three factors determine whether a substance belongs on Schedule I:

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

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

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

As further explained below, it is my opinion that the science strongly supports a conclusion that marijuana has a high potential for abuse, has no currently accepted medical use in the United States, and that sufficient assurances of safety for use of marijuana under medical supervision are lacking. Based on my training, experience, and research in the field, the science strongly supports the conclusion that marijuana has met, and continues to meet, the criteria for inclusion in Schedule I of the Controlled Substances Act.

III. THE SCIENTIFIC PROCESS FOR DETERMINING MEDICAL USE

14. It is important to understand that the United States has long adhered to a scientifically driven process for reviewing and approving medicines to ensure that they are both safe and effective before they are released to the public. It is this process—which includes large teams of chemists, pharmacologists, physicians, microbiologists, veterinarians and even lawyers—and not individual physicians or anecdotal information from users, that determines whether a product has accepted medical uses, and may be safely used as a medicine by the general public.

15. In the past 100 years, the United States developed a scientific process to ensure that

proposed medicines are both safe and effective. Starting in the 19th century, chemists began to isolate pure chemicals from medicinal plants, study them, and make safer variants: the active drugs morphine from the opium poppy, cocaine from the coca bush, digitalis from the foxglove plant, salicylic acid (converted to aspirin) from willow bark, ephedrine from the Ma Huang plant, and quinine from cinchona bark were isolated (or, at times, further modified). Behind this new science was the dawn of rational development of medications. Chemists and physicians reasoned that it was wiser to isolate a pure compound from a plant, remove it from other chemicals and contaminants that may be toxic or interfere with its actions, and administer a pure drug of known quantity, in a safe dosage range. Another advantage of isolating the active constituents of botanical plants was to enable discovery of their mechanisms of action, thereby placing each botanically-derived compound on a firm scientific base. Isolated compounds led to the discovery of receptors (targets) and signaling systems of opiates, cannabinoids, hallucinogens, nicotine, cocaine, methamphetamine and a host of other psychoactive drugs, which resulted in an explosion of information on disease processes, mechanisms of brain reward, hallucinations, and therapeutic benefit, and enabled rational design of improved medications. A relevant example is the isolation of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) from the marijuana plant in the 1960's. It is now known that mechanisms of action of intoxicant THC and the non-psychoactive CBD are distinct; CBD can oppose some of the memory and behavioral impairment of THC, CBD does not impair memory as does THC, and their therapeutic indications may differ. This compelling evidence supports the need to continue the process and methodology of modern medicine with respect to the marijuana plant. The evolution of marijuana research is following the same principles as drug therapies in general, following the discovery of its active chemicals in the early 1960's. Science should continue to isolate pure cannabinoids in the marijuana plant and evaluate them separately to determine whether they have medicinal value, all through an evidence-based process designed to protect patients and the general public.

16. Although more than 30% of current therapeutic drugs are plant-derived, no one currently eats or smokes foxglove plants to treat a heart condition, chews cinchona bark to alleviate malaria symptoms, or eats opium poppies to relieve post-surgical pain. Instead, scientists have isolated compounds, identified safe and effective dose ranges, and developed medicines from these

plants to treat these conditions. It is as irrational to smoke marijuana for medicinal purposes in the 21st century as it was to chew bark to relieve a headache or smoke opium for pain in the 20th century.

17. In 1938, our safe drug supply system advanced once again, as the newly formed FDA required strong scientific evidence of both effectiveness and safety for drug approval. The creation of the FDA was in response to numerous examples of illness or death resulting from entrepreneurs who marketed dangerous drugs, tinctures, or other concoctions with unsubstantiated claims for medical benefit or safety. The FDA currently has a well-developed and rigorous evaluation and approval process for determining whether scientific evidence is adequate to support claims that a specific drug is effective and safe for use in diagnosing, mitigating, treating, or curing disease. When such claims are made about a substance, it is considered a drug under section 201(g)(1)(B) of the Act and is subject to regulation as such.

18. The Federal Food, Drug, and Cosmetic Act requires that new drugs be shown to be safe and effective for their intended use before being marketed in this country. FDA's drug approval process begins after a producer identifies a handful of compounds that may be effective and safe in cells, in an animal model of disease and in toxicity studies. When this phase is over, the drug developers apply to the FDA for permission to study the drug in humans.

19. Before conducting testing in humans of a drug that has not been approved by the FDA, an investigator submits an investigational new drug (IND) application, which is reviewed by the FDA. An IND includes protocols describing proposed studies, the qualifications of the investigators who will conduct the clinical studies, and assurances of informed consent and protection of the rights, safety, and welfare of the human subjects. The FDA reviews the IND to ensure that the proposed studies, generally referred to as clinical trials, do not place human subjects at unreasonable risk of harm. The FDA also verifies that there are adequate assurances of informed consent and human subject protection.

20. Well-controlled human trials are performed in at least three phases, the first to measure the safety of a range of doses, usually in less than 100 healthy volunteers or subjects. These Phase I studies carefully assess how to safely administer and dose the drug with an emphasis on evaluating the toxic manifestations of therapy, how the body distributes and degrades the drug, and

how side-effects relate to dose. Phase II clinical studies monitor the effectiveness of the drug at a range of doses for a particular indication and to determine common, short-term side-effects. Phase II usually involves a few hundred subjects. Once Phase II is complete, Phase III trials assess the safety and effectiveness of the drug in randomly assigned, larger patient populations (usually from several hundred to several thousand). The testing is conducted consistent with the protocol and is usually double blinded,[1] in which case neither the person administering the drug nor the patient know whether they are given the investigational drug or a control (which could be a placebo or another already-approved product).

21. These studies establish efficacy for a specific medical indication, examine additional uses, may provide further safety data including long-term experience, and consider additional population subsets, dose response and other factors. Once Phase III trials are completed, the sponsor submits the results of all the relevant testing to FDA in the form of a New Drug Application (NDA). FDA's medical officers, chemists, statisticians, and pharmacologists review the application to determine if the sponsor's data in fact show that the drug is both safe and effective. The drug's manufacturing process is evaluated to confirm that the product can be produced consistently with high quality. It is common to allow subjects in Phase II and III studies to continue on a therapy if it seems to be providing benefit. This practice provides long-term safety information at an early stage in this process.

22. The FDA insists on a vast array of information on the drug from the manufacturer that shows all the pre-human research, the scientific evidence that drug is effective at a fixed dose range in humans, proof that the drug is pure, that it can be manufactured indefinitely to produce the same chemical in pure form with inert fillers and uncontaminated with microbes, that the tested shelf life is known, what percent enters the blood stream, what percent gets to its target, how it is metabolized and cleared by the body, how long it takes for the body to clear, how often it should be taken, how long it can be safely taken, whether side effects are acceptable, and a myriad of other criteria to ensure patient safety. With this scientific documentation at hand, the FDA then decides whether to approve the drug for a specific condition, what information should be included in the package insert, and other labeling

[1] Double-blinded studies are preferred, except where doing so is either impossible or unethical.

decisions. If a drug product is to be marketed, these disciplined, systematic, scientifically conducted trials are the best means to obtain data to ensure that drug is safe and effective when used as indicated. Efforts to bypass the FDA drug approval process are adverse to public health because they are likely to expose patients to unsafe and ineffective drug products. Results of controlled clinical trials are determined by evidence-based medicine, allowing physicians and patients to use therapies with a clear understanding of their benefits and risks and, in some cases, a basis for strong public health recommendations for treatments.

23. An example that illustrates the importance of conducting clinical trials are the results of an NIH Women's Health Initiative (WHI) study of estrogen and progesterone in treating post-menopausal women (more than 16,000 women). As extracted from testimony by Dr. Robert J. Meyer, M.D. Director, Office of Drug Evaluation II, Center for Drug Evaluation and Research Food and Drug Administration in 2004: "this rigorous clinical trial was done to confirm the widely held belief that estrogen/progesterone therapy in post-menopausal women would significantly reduce the risk of cardiovascular events, such as heart attacks and strokes, with some hope that this post-menopausal therapy might lessen the onset of Alzheimer's disease. These widely held beliefs were based on scientific evidence that was not from clinical trials, such as epidemiology. On the strengths of these beliefs, post-menopausal hormone therapy was very widely used and growing in popularity. The WHI trial of post-menopausal estrogen/progesterone preceded but was stopped early due to an excess of harm in women taking these drugs compared to placebo…women given the active drugs were more likely to suffer heart attacks and strokes and appeared to be more likely to develop dementia. This study not only failed to prove the widely held notion that this therapy was good for preventing these types of occurrences, but actually confirmed harm. These important results have led to significant changes in the use of post-menopausal hormones." Similarly, laetrile was approved via ballot initiatives in over 15 states during the 1970's, until it was shown in carefully controlled clinical trials, spearheaded by NIH and FDA, to be ineffective and to carry considerable risk from cyanide poisoning (Milazzo et al, 2011).

24. The FDA also protects patients after it has approved a drug. If there is evidence of newly emerging unacceptable side effects, the FDA can modify prescribing practices, issue a "Black Box" warning, or withdraw the drug. If a pharmaceutical company makes an unsupported claim that its

approved drug can treat a different disease, the FDA can and has fined companies (more than $10 billion in past few years).

25. The FDA process has protected the American public from ineffective or even dangerous drugs for more than 75 years. Drugs that do not meet this standard do not have accepted medical uses in my opinion.

26. The marijuana plant, like other plants, is not reasonably amenable to analysis by the current, established FDA approval process. While many of our medicines have their origin in plant-derived compounds, I am unaware of any whole plant that has been approved for medical use in recent times. A medicine is something of known and reproducible chemistry, and which can be provided in pure form(s) and precise dosage amounts. Marijuana does not meet any of the FDA criteria for a safe drug: It is made up of more than 400 chemical compounds, of which over 80 are cannabinoids, the majority of which have unknown effects or side effects. Nor have there been systematic or reliable studies of marijuana's side-effects or adverse effects (e.g. addiction) over extended periods of use for chronic medical conditions, a critical factor in determining whether a drug may be safely used under a doctor's supervision.

IV. DEA's SCHEDULING PROCESS

27. My opinion is that, from a scientific perspective, there is a strong basis for concluding that marijuana appropriately remains a Schedule I substance at this time. Before evaluating the specific reasons for this opinion, it is important to understand the Controlled Substances Act's Scheduling process.

28. The Controlled Substances Act delegates to the Attorney General the authority to schedule, de-schedule, or reschedule controlled substances. The Attorney General has, in turn, delegated the review process to the Drug Enforcement Administration (DEA), which must work closely with the FDA and NIDA in making its determination on scheduling. Although the Attorney General or DEA may undertake this Scheduling inquiry at any time, it is most typically done through a Scheduling petition. It is my understanding that a Scheduling petition is currently pending before DEA and FDA, and was filed by the Governors of Washington and Rhode Island.

29. Marijuana was placed on Schedule I by Congress in 1970, and DEA has periodically reviewed that decision, including as recently as 2011. Its decision, after consultation with FDA and

others, has always been to maintain marijuana on Schedule I. *See* Denial of Petition To Initiate Proceedings To Reschedule Marijuana, 76 F.R. 40552 (July 8, 2011), attached hereto as Exhibit C. It is my understanding that this decision was upheld by the United States Court of Appeals for the District of Columbia Circuit in 2013 against a challenge that it was "arbitrary and capricious." *Americans for Safe Access v. Drug Enforcement Admin.*, 706 F.3d 438 (D.C. Cir. 2013).

30. DEA's process, which is described in further detail in the Federal Register notice announcing its 2011 decision not to reschedule, is scientifically-driven and evidence-based. It is my opinion that DEA, in conjunction with FDA and NIDA, was well-justified in reaching the conclusion that the safety assurances required for medicines were lacking when they denied the most recent petition to reschedule marijuana in 2011. Under the factors set forth below for evaluating whether to schedule a substance, as well as the factors for whether a substance meets Schedule I criteria, the DEA's decisions to maintain marijuana on Schedule I (including in 2011) are strongly supported by the science.

31. The Attorney General (or his delegate) may, after recommendation from HHS, decide to add a substance to a schedule or to transfer a scheduled substance to another schedule if it is found that such drug or other substance has a potential for abuse. A substance may also be removed from the schedule if it is determined that the substance does not meet the requirements for inclusion in any schedule. The recommendation to schedule a substance (as opposed to the decision of *where* to schedule a substance) is made on the basis of the following criteria:

(1) Its actual or relative potential for abuse[2]

(2) Scientific evidence of its pharmacological effects;

(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; and

(8) Whether the substance is an immediate precursor of a substance already controlled.

[2] Any drug having a stimulant, depressant, or hallucinogenic effect on the central nervous system, is considered to have abuse potential.

21 U.S.C. § 811(c). In addition, the United States has obligations to control marijuana's use under international treaties, conventions, and protocols.

32. With regard to the specific question of whether a non-FDA-approved controlled substance has a currently accepted medical use in treatment in the United States, DEA has set forth a five-part test:

(1) The drug's chemistry must be known and reproducible;

(2) There must be adequate safety studies;

(3) There must be adequate and well-controlled studies proving efficacy;

(4) The drug must be accepted by qualified experts; and

(5) The scientific evidence must be widely available.

57 Fed. Reg. 10499, 10504-10506 (1992). Failure to meet any of these five prongs precludes a finding that the drug has a currently accepted medical use in treatment in the United States for purposes of the Controlled Substances Act. *Id.*; *see also Alliance for Cannabis Therapeutics v. DEA*, 15 F.3d 1131, 1135 (D.C. Cir. 1994); *Americans for Safe Access v. DEA*, 706 F.3d 438, 449-450 (D.C. Cir. 2013). This five-part test is consistent with the core criteria of the FDA drug approval process.

33. FDA engages in a rigorous process in evaluating the eight factors set forth in 21 U.S.C. § 811(c), the factors for particular schedules set forth in 21 U.S.C. § 812(b), and, where appropriate, the five-part test for determining whether a substance has a currently accepted medical use in treatment in the United States. In so doing, FDA focuses exclusively on science. It then makes a recommendation to DEA.

34. By following this rigorous scientific process, for which judicial review is available, the scientific community can be confident, to the degree possible, that scientific decisions are being made on the basis of scientific data and judgment. This is the hallmark of our system, and we should not deviate from it for marijuana simply because there are anecdotal tales of success, greater social acceptability for use of marijuana, or information derived from controlled clinical trials of inadequate sample sizes or evaluation of adverse effects. While Congress certainly has the authority to make such a political and/or policy judgment, the role of the scientists and regulators at FDA and DEA must remain scientific and regulatory. There is no doubt that there is currently a rational basis for maintaining marijuana on Schedule I.

V. SPECIFIC OPINIONS

35. Marijuana continues to meet the criteria for Schedule I under the Controlled Substances Act. The basic supporting data and reasons for my opinions are set forth below. Given the wealth of supporting research and scientific information, it is not reasonable to list every detail. Such details, if needed, can be provided as part of my oral testimony.

A. There is Strong Scientific Support for Concluding that Marijuana Has High Potential for Abuse

36. The current data and scientific research strongly support the conclusion that marijuana both has a high potential for abuse, and is actually abused. This is particularly true in young people. The earlier one first uses marijuana, the more likely one is to abuse marijuana. As an example, the prevalence of a marijuana (cannabis) use disorder among persons who initiate marijuana use at age 14 or younger (13.2%) is six times higher than those who initiate marijuana use at age 18 (2.2%) or older (NSDUH 2013). Marijuana is addictive in approximately 9-10% of users and 25-50% of daily users become addicted. It should be apparent that people who use marijuana for chronic conditions will use it daily and over an extended period, and are thus at high risk for addiction. The diagnostic and statistical manual of Mental Disorders ("DSM") of the American Psychiatric Association has designated that marijuana is addictive, and currently recognizes a specific Cannabis Dependence (Use) Disorder. (*See* DSM-IV, § 304.30, and DSM-V). In the DSM-IV and -V, marijuana fulfills the criteria of a full spectrum of a substance use disorder, from abuse (hazardous use, social and interpersonal problems related to use, neglected major roles and responsibilities), to addiction (withdrawal, tolerance, uncontrollable use, unintentional use of larger amounts and for longer periods of time than intended, repeated unsuccessful attempts to quit, psychological/physical problems related to use, activities given up, craving). As the DSM recognizes, individuals with this disorder have compulsive use and associated problems, use of the drug often interferes with family, school, work responsibilities, recreational activities, and chronic use persists despite knowledge of related physical or psychological problems, such as chronic cough, excessive sedation, difficulty concentrating, and a decrease in goal-oriented activities.

37. The DSM-V also recognizes that marijuana use occurs along a spectrum of severity of

adverse effects. Abuse occurs even if the hallmarks of addiction are not involved. A criteria count (from two to eleven) is used as an overall severity indicator, such that mild (two to three criteria), moderate (four to five), and severe (six or more) disorders are documented.

38. Marijuana is the most widely used illicit substance in the United States, and more Americans (4.3 million) harbor a medical (DSM-IV) diagnosis of marijuana abuse/addiction than any other illicit drug. Many more youth are DSM-IV positive for a marijuana use disorder than for an alcohol use disorder, as a percentage of those in treatment. Treatment admissions for youth aged 15 to 17 most frequently reported marijuana (71.9 %) or alcohol (17.7%) as their primary substance of abuse. About 14.3% of older adolescent admissions reported first using their primary substance of abuse at age 11 or younger, and over half (56.3%) reported first using their primary substance between the ages of 12 and 14. Marijuana treatment may require billions of dollars in treatment needs nationally. Although treatment admissions for alcoholism and cocaine addiction declined between 1992 and 2007, marijuana use disorder admissions climbed significantly during the same period. Similarly, emergency department mentions have also increased significantly between 2004 and 2008.[3]

39. Although addiction, habituation, and abuse do not necessarily require physiological or physical symptoms during withdrawal, abstinence in heavily addicted marijuana users unmasks physical and psychological neuroadaptation, manifest by a withdrawal syndrome. The validity of marijuana withdrawal has been demonstrated in preclinical, clinical, and epidemiological studies. Marijuana withdrawal is reported by up to one-third of regular users in the general population and by 50%–95% of heavy users in treatment or research studies. The clinical significance of marijuana withdrawal is demonstrated by use of marijuana or other substances to relieve it, its association with difficulty quitting, and worse treatment outcomes associated with greater withdrawal severity. It is true that marijuana is not as likely to cause death by overdose as other scheduled substances, but it is still a dangerous substance for brain, body, and behavior.

40. The scientific research shows that marijuana literally changes the brain, with abnormalities detected both in the short term and the long term. Marijuana also adversely affects brain function over the short term and long term, and compromised brain function has shown to be correlated

[3] *See http://www.samhsa.gov/data/2k12/TEDS_061/TEDS_061_LateAdolescents_2012.htm*

with the changed brain. Smoking marijuana is intoxicating in the short term, but can also produce residual cognitive deficits (on learning and memory), which may persist. These deficits are readily quantified, are exaggerated in certain populations, such as schizophrenics. Adolescent and long term use of marijuana is also associated with a significant reduction in IQ measured at age 38, and also reduced motivation and increased prevalence of psychosis later in life.

41. The mortality of patients with a substance use disorder was assessed in patients hospitalized in California from 1990 to 2005 with medical diagnoses of methamphetamine (n = 74,139), alcohol (n = 582,771), opioid (n = 67,104), marijuana (n = 46,548), or cocaine use disorders (n = 48,927). Groups were followed for up to 16 years and age-, sex-, and race-adjusted standardized mortality rates (SMRs) were generated. The SMR is the ratio of mortality rates comparing people that harbor a substance use disorder to matched controls. Although the opioid and methamphetamine cohorts had the highest SMR (5.71, 4.67), marijuana was third in mortality rate (3.85), slightly higher than alcohol (3.83) or cocaine (2.96). The reasons for the higher mortality rates among populations with a marijuana use disorder remain unknown.

42. Marijuana use can compromise a student's ability to focus in class for several days, expose a construction worker to greater risk of injury, engender concentration problems, and reduce motivation. There is good reason why it is unacceptable for soldiers, airline pilots, nuclear power plant operators, physicians, and law enforcement officers to test positive for marijuana use at any time, rather than only on the job.

43. A 2009 National Highway Traffic Safety Administration (NHTSA) report showed that more people are driving on weekend nights under the influence of marijuana (8.3%) than alcohol (2.2%). There is a significant increase nationally in traffic fatalities involving drivers that tested positive for marijuana (Brady JE and Li G, *Trends in Alcohol and Other Drugs Detected in Fatally Injured Drivers in the United States*, 1999-2010, Am J Epidemiol. 17: 692-699, 2014) and a large increase in fatalities involving marijuana-positive drivers since marijuana has become more available in states like Colorado. (Salomonsen-Sautel S, Min SJ(2), Sakai JT, Thurstone C, Hopfer C., *Trends in fatal motor vehicle crashes before and after marijuana commercialization in Colorado*, Drug Alcohol Depend. 2014 Apr 23).

44. Marijuana has a high potential for abuse because many users seek its euphoric effects. That is, even if some people may use marijuana believing in good faith that it is helping with their symptoms, many other people use marijuana to get high and not for any other purpose. As to medicinal claims, a significant proportion of older cancer patients who had no previous experience with marijuana refused to continue its use because the subjective psychoactive effects were too unpleasant. For such reasons, there is significant doubt whether smoked marijuana will find widespread clinical application, except among those who have previously used it for nonmedical purposes (Kalant, 2008).

45. In brief, there is no question that extensive data and practical experience support the conclusion that marijuana has a high potential for abuse, and is actually abused. This does not mean that policy makers could not choose a different outcome, and determine that the risks and consequences of marijuana abuse are outweighed by other factors. *See, e.g.*, 21 U.S.C. § 802(6) (alcohol and tobacco exempted from Controlled Substances Act); *see also* U.S. Const. Amend XXI (repealing prohibition on alcohol). But there is more than adequate support to reach the conclusion that marijuana has a high potential for—and high actual incidence of—abuse. Further support for, and explanation of this position may be found in the Secretary of Health and Human Service's recent conclusions on marijuana's potential for abuse. *See* 58 F.R. 20038, 20039 (April 18, 2001); 76 F.R. 40552 (July 8, 2011).

B. There is Strong Scientific Support for Concluding that there is No Currently Accepted Medical Use for Marijuana.

46. Merely because some medical practitioners support the use of marijuana as medicine, or clinically controlled, but small, trials report therapeutic benefit, does not mean that there is a currently accepted medical use for the drug. The FDA has not approved marijuana as a medicine. At this time, there are insufficient high quality clinical studies to ensure the safe and effective use of marijuana as medicine. Also, contrary to modern medications, marijuana is a complex mixture of hundreds of chemicals of unknown concentrations, pharmacological effects, and side-effects, and is delivered mainly by an unacceptable route of administration: smoking. It thus has no currently accepted medical use.

47. The FDA's role in the regulation of drugs, including marijuana and marijuana-derived products, includes review of applications to market drugs to determine whether proposed drug

products are safe and effective for their intended indications. The FDA's drug approval process requires that clinical trials be designed and conducted in a way that provide the agency with the necessary scientific data upon which it can make its approval decisions. Without this review, the FDA cannot determine whether a drug product is safe and effective. It also cannot ensure that a drug product meets appropriate quality standards. For certain drugs that have not been approved by the FDA, such as marijuana, the lack of FDA approval and oversight means that the purity and potency of the drug may vary considerably.

48. The FDA supports research into the potential medical use of marijuana and its constituents through cooperation with other federal agencies involved in marijuana research. Conducting clinical research using marijuana involves interactions with other federal agencies. The FDA reviews the Investigational New Drug (IND) application and the research protocol submitted by the applicant. The Drug Enforcement Administration (DEA) reviews the registration application filed by the researcher. The National Institute on Drug Abuse (NIDA) operates pursuant to the Single Convention on Narcotic Drugs. NIDA has been designated with the responsibility to supply research-grade marijuana to researchers.

49. Conducting clinical research using marijuana involves interactions with three federal agencies. This includes: obtaining the marijuana for research from NIDA within the National Institutes of Health; review of an IND application and the research protocol by the FDA; and a site inspection and research registration by DEA.

50. NIDA's role is to obtain the marijuana for research. NIDA's marijuana supply program operates pursuant to the Single Convention on Narcotic Drugs, which imposes certain obligations related to governmental oversight of marijuana cultivation. NIDA contracts with the University of Mississippi to grow marijuana in a secure environment for use in research studies. The FDA reviews an IND application, as noted above. This required step gives regulators and researchers a path to follow that includes regular interactions with the FDA to support efficient drug development while protecting the patients who are enrolled in the trials. DEA is required to determine whether the researcher will have adequate controls in place to safeguard against diversion of the drug. 21 U.S.C. § 823(f). For more information. *See* 21 C.F.R. § 1301.18 (DEA Research

Protocols).

51. In reality, marijuana is a botanical product in that it is composed of plant materials. Because marijuana is a botanical product, there are substantial obstacles to meeting the statutory standard for approval. For instance, FDA would expect an NDA for a synthetic or highly purified drug to identify the active ingredient. In the context of a proposed marijuana drug product, it will be particularly challenging to identify the active ingredient because marijuana is made up of more than 400 chemical compounds, including more than 80 are cannabinoids, the majority of which have unknown effects or side effects. It is much more likely that effective compounds (if any) will be identified, isolated, purified, and individually approved as medicines.

52. Marijuana smoke contains significant amounts of toxic chemicals, including ammonia, hydrogen cyanide and nitric oxide. The doses of active ingredients are unknown to patients and physicians, and there is no guarantee of product purity or absence of microbes or pesticides that can produce infections and other disease. Further, the percentage of THC that enters the body is unknown and can vary widely if the marijuana is smoked (10-50%) or eaten (~6%+), with effects lasting for unknown times. It is virtually universally recognized among physicians and researchers that smoking anything is harmful to health. Standard medicines are not smoked, but enter the body in many other ways (pill, injection, topical creams, patches, inhalants, eye drops, suppositories, etc.) with the amount entering the blood stream evaluated in clinical trials and doses carefully chosen to account for rate of entry. When the effects of orally administered cannabis extract, THC, and placebo on both appetite and quality of life were compared in a large, double-blinded, controlled trial of patients with cancer-related anorexia-cachexia syndrome, no significant differences in patients' appetite or quality of life were found between cannabis extract and THC at the dosages investigated. An independent data review board recommended termination of recruitment because of insufficient differences between study arms. (Strasser et al, 2006).

53. The chemistry of marijuana is not uniform. It varies from strain to strain and even from plant to plant. In other words, the term "marijuana" is virtually useless to one analyzing whether there are medical applications. In controlled clinical trials with marijuana, THC and possibly CBD content are the only composition of matter provided. There is too great a variance among the existence and

concentrations of compounds within the variety of plants sold in dispensaries to produce reliable indications for marijuana's use as a medicine. The precedent for modern medicine of the past 100 years is clear: each compound within the marijuana plant requires extraction, isolation, purification to reproducible pure forms for evaluation for possible medical applications. Only by systematic evaluation of pure compounds, and possibly by designing variants that are safer and more effective (for example, the design of lidocaine to replace cocaine as a local anesthetic) can safe, controllable, and effective doses of cannabinoids be introduced into modern medicine. Indeed, the FDA has approved a product (Marinol) which contains THC (delta-9-tetrahydrocannabinol), the most active constituent of marijuana, to treat nausea caused by chemotherapy and wasting disease (extreme weight loss) caused by AIDS. The FDA has also approved Nabilone (Cesamet) which contains a synthetic cannabinoid similar to THC and is used for the same purposes. Sativex, which contains approximately equal parts THC and cannabidiol (CBD), is currently approved in the UK and several European countries to treat spasticity caused by multiple sclerosis (MS), and it is now in Phase III clinical trials in the U.S. and on a "fast-track" to expedite development and review of its effectiveness and safety in treating cancer-related pain. Although it has not yet undergone clinical trials to establish its effectiveness and safety (necessary to obtain FDA approval), a CBD-based drug called Epidiolex has recently been developed to treat certain forms of childhood epilepsy.

54. It is possible, and perhaps probable, that science may discover medicines from the compounds within the marijuana plant in the years to come. Those compounds would then be evaluated by the FDA-approval process to ensure that they are effective and may be safely used. But this does not mean that the marijuana plant, composed of more than 400 compounds, is itself medicine. A clinical trial comparing the effects of smoked marijuana with dronabinol (THC alone) suggested that, under controlled conditions, marijuana and dronabinol decreased pain, but dronabinol produced longer-lasting decreases in pain sensitivity and lower ratings of abuse-related subjective effects than marijuana. Another pilot study measuring daily caloric intake and body weight in HIV-positive marijuana smokers compared placebo with marijuana and dronabinol. It found that marijuana and dronabinol effects were comparable, and that both dronabinol and marijuana were well-tolerated and produced substantial and comparable increases in food intake. All cannabinoid conditions

produced significant intoxication, except for low-dose dronabinol. To the best of my knowledge, no other clinical trials have compared smoked marijuana to oral/spray THC or THC/CBD for other medical conditions, leaving the issue of whether smoked marijuana confers any advantage in efficacy and safety unresolved.

55. In reality, there is no such thing as "medical marijuana"; that is, there is not a particular type of marijuana used for medicinal purposes, let alone for a specific, proven medical purpose. Physician recommendations for medicinal use of smoked marijuana (obtainable in a dispensary) are not grounded in systematic, evidence-based research, which is the hallmark of our system.

56. For these and other reasons, the major medical associations do not endorse the use of marijuana as medicine, including the American Medical Association, the American Society for Addiction Medicine, the American Psychiatric Association, the American Cancer Society, the American Glaucoma Society, the American Academy of Ophthalmology, the American Academy of Pediatrics, the National Multiple Sclerosis Society, the British Medical Association, and Canadian Society of Addiction Medicine. A substantial majority—perhaps the vast majority—of scientists familiar with the literature and research agree that, at this time, marijuana does not have medical application. Future medical applications that might be derived from marijuana, if any, will be discovered through isolation of particular compounds that can be administered in pure, safe, and reliable dosages.

57. In 2013, the AMA voted to confirm its position that "cannabis is a dangerous drug and as such is a public health concern." According to the AMA Policy on Medical Marijuana (November 2009), the AMA "calls for further adequate and well-controlled studies of marijuana and related cannabinoids" and urges all actions, including marijuana's scheduling, to promote study and scientific research on marijuana, rather than uninformed action one way or the other.

58. The American Psychiatric Association policy on medical marijuana is as follows:

- There is no current scientific evidence that marijuana is in any way beneficial for the treatment of any psychiatric disorder. In contrast, current evidence supports, at minimum, a strong association of cannabis use with the onset of psychiatric disorders. Adolescents are particularly vulnerable to harm, given the effects of cannabis on neurological development.

- Further research on the use of cannabis-derived substances as medicine should be encouraged and facilitated by the federal government. The adverse effects of marijuana, including, but not limited to, the likelihood of addiction, must be simultaneously studied.
- Policy and practice surrounding cannabis-derived substances should not be altered until sufficient clinical evidence supports such changes.
- If scientific evidence supports the use of cannabis-derived substances to treat specific conditions, the medication should be subject to the approval process of the FDA. Regarding state initiatives to authorize the use of marijuana for medical purposes:
- Medical treatment should be evidence-based and determined by professional standards of care; it should not be authorized by ballot initiatives.
- No medication approved by the FDA is smoked. Marijuana that is dispensed under a state-authorized program is not a specific product with controlled dosages. The buyer has no way of knowing the strength or purity of the product, as cannabis lacks the quality control of FDA-approved medicines.
- Prescribers and patients should be aware that the dosage administered by smoking is related to the depth and duration of the inhalation, and therefore difficult to standardize. The content and potency of various cannabinoids contained in marijuana can also vary, making dose standardization a challenging task.
- Physicians who recommend use of smoked marijuana for "medical" purposes should be fully aware.

APA, *Position Statement on Marijuana as Medicine* (December 2013).

59. Both inadequate clinical trials and anecdotal evidence reporting improvement from marijuana use are insufficient to establish "currently accepted medical use." The FDA's rigorous process for making these determinations must be followed, or there is a risk of a return to the days of ineffective or dangerous elixirs. The United States' medical system, indeed the global system, has benefitted tremendously from this scientific approach and progress. Science, and a scientifically-based approval process, should continue to be the central factor in evaluating and approving substances for use as medicine. If safe medical applications for phytocannabinoids (cannabinoids made by marijuana plants) or synthetic cannabinoids (created by chemists) or novel drugs that alter cannabinoid signaling systems in the body, are revealed, then this scientific process will prove no barrier to their approval.

60. As noted above, DEA also uses a five-part test to evaluate whether a drug that is not approved by FDA has a "currently accepted medical use." All five factors must be met:

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

These factors are consistent with the core requirements for FDA approval, and the agency recognized as much in adopting the five-factor test. *See* 57 FR 104504. It is my opinion that the marijuana plant fails to meet any of these requirements. As noted above and below, there are no adequate safety studies for daily functioning (e.g. driving, working, attentiveness at school, learning and memory) or long-term use, nor are there adequate and well-controlled randomized double-blinded trials (RCT) demonstrating efficacy in general (drug-naïve) populations. The majority of studies recruit experienced marijuana users as subjects for a number of reasons, including concerns of unacceptability and drop-out rates among marijuana-naïve subjects. Considering the concerted effort during the 20th century to minimize or eliminate psychoactive effects of any medication, clinical trials evaluating marijuana should include side-by-side comparisons with isolated cannabinoids or alternative drugs (e.g. for chemotherapy-induced nausea or glaucoma). The most that can be said for marijuana in this regard is that the safety studies (particularly for long-term uses) are lacking, and that the efficacy studies are insufficient to meet FDA standards. Even assuming that there were adequate efficacy studies, marijuana poses significant challenges. Smoking is not an appropriate drug delivery system. Approval of a complex plant with hundreds of chemicals is not a progressive step in the evolution of modern medicine, but rather regressive. Marijuana would also need several studies comparing it to alternatives.

61. Moreover, marijuana's chemistry is a major hurdle if regulatory agencies adhere to consistent criteria in the drug approval process and standards for medications: the plant (other than specific suppliers, e.g. NIDA) is simply too variable to meet this standard at this time. For these and other reasons, marijuana is not an accepted medicine among qualified experts at this time; at best, there is sharp dispute as to marijuana's utility and safety. This is not to say that isolated compounds within marijuana have not been accepted as medicine—they have (e.g., Marinol). But there is no agreement among qualified experts that marijuana itself is an acceptable medicine. Finally, the scientific data supposedly supporting marijuana's use as medicine is not widely available. For the most part, it is lacking. Further, most studies used to support marijuana's treatment as medicine are inadequate (not RCT, small number of subjects, side effect evaluation inadequate) or are described only in abstract form or summarized together with data from isolated cannabinoids. Raw data and data transparency are critical, and would permit the scientific community to evaluate the information

first hand. Thus, it is my opinion that marijuana fails each of the five criteria. It does not have a currently accepted medical use for FDA purposes, nor does it have a currently accepted medical use under DEA's five-part test meant to approximate the FDA standards.

62. While some physicians may believe that marijuana does have medical uses, the current, reliable scientific research does not support this view. Based on my own research and my familiarity with the research of others, and the stringent FDA process, it is my view that, although the research is ongoing, the marijuana plant itself has no place in modern medicine, and no medical indications that fulfill current safety and efficacy standards.

C. There is Strong Scientific Support for Concluding that Adequate Assurances that Marijuana Can be Safely Used under Medical Supervision is Lacking.

63. The issue of safe use of marijuana under medical supervision is largely subsumed within the prior discussion about marijuana's supposed medical uses. Indeed, part of the FDA process is to determine that drugs can be safely used in this manner. With no reliable information about the composition of the varying strains of marijuana, and even the variations from plant to plant, safe use simply cannot be established. In other words, a substance cannot be used safely, even under medical supervision, if one does not have an adequate understanding of the composition of the substance. Levels of the psychoactive substance within marijuana (delta-9 THC) can vary from below 1% to above 30%. Other compounds in marijuana botanicals (e.g. cannabidiol) may also vary widely, depending on the breed of the plant. They are simply too many variables to assure safety to potential patients at this time, and to assure that drug-drug interactions will be harmless.

64. The psychoactive effects of marijuana represent a significant obstacle to designing double-blinded clinical trials. Recent studies suggest that between 20% and 50% of individuals report paranoia, persecutory ideas, or hallucinations while under the influence of marijuana (Green et al., 2003; Reilly et al., 1998). Side effects of marijuana have to be viewed in the context of immediate effects and after repeated long term use. Ranganathan and D'Souza (2006) examined studies that dealt primarily with effects on memory, and found dose-related impairments of immediate and delayed recall of information presented while the subjects were under the influence of the drug. Various phases of learning and memory were affected, as were signs of depersonalization, distorted sensory perception,

and altered time perception. Crean et al. (2011) reviewed executive functions in marijuana users (attention, concentration, decision-making, impulsivity, self-control, reaction time, risk taking, verbal fluency and working memory) and found all of these functions impaired acutely in a dose-dependent manner. In long-term users seen after periods of withdrawal of at least 21 days, some components of executive function recover completely, while decision-making, concept formation and planning deficits persist. Persistent deficits are more likely to be detected in those who began regular marijuana use early in adolescence, or who used marijuana more heavily and for a longer time. These conclusions agree with clinical impressions based on population studies (e.g., Kalant, 2004, Kalant, 2013, Hall and Degenhardt, 2014, Degenhardt et al, 2013, Degenhardt and Hall 2008).

65. In addition, the only indications for medical use of marijuana offered by its proponents have been for chronic conditions (e.g. AIDS neuropathy, AIDS wasting, multiple sclerosis, chronic pain), but I am aware of no long term studies examining the effects of chronic marijuana use among people using marijuana for medical conditions, with particular voids in long term progression to addiction or cognitive impairment.

66. Especially in view of marijuana's negative side-effects, one simply cannot be assured that marijuana can be safely used, even under medical supervision, for long term open-ended use. Current estimates are that 25-50% of daily marijuana users develop an addiction to marijuana. Important information about side-effects and safety could be collected if marijuana went through the normal evaluation for approval as a medicine. The FDA collects information from "adverse event reports," yet adverse event reports regarding marijuana use are extremely limited at this time because it has not gone through FDA's process. Further information on the potential adverse effects of using marijuana and its constituents can come from clinical trials using marijuana that have been published (if interrogated), as well as from spontaneously reported adverse events sent to the FDA.

67. For heavy users, other side effects can include altered brain structure and brain circuits impaired short-term memory, compromised judgment and decision-making, and mood effects that can range from severe anxiety manifest as paranoia or even psychosis, especially after high-doses. Marijuana can reduce motor coordination alone or combined with alcohol, slow the reaction time of drivers. Marijuana smoking can cause or worsen breathing problems such as bronchitis or chronic

cough and evidence is increasing that it may cause serious cardiovascular problems in some users. Regular use of marijuana for asserted medical purposes is so recent that its long-term effects on seriously ill people cannot be adequately predicted at this time, especially among those that harbor cognitive impairment as a consequence of their the disease (e.g HIV-AIDS, multiple sclerosis, Alzheimer's, certain seizure disorders). The impact of long-term use on young people, whose frequent use for asserted medical reasons is increasing rapidly, cannot be adequately predicted at this time either. Young people are particularly vulnerable to the adverse effects of marijuana. Especially if used regularly by adolescents, who experience a period of rapid brain development, marijuana may result in long-term or irreversible decreases in cognitive ability and intelligence. Marijuana use during pregnancy may also be associated with brain and behavioral deficits in babies. Further study of the long-term effects on these vulnerable populations is absolutely required before one can claim that marijuana has adequate safety and efficacy studies to be evaluated as a medicine.

68. In summary, the immediate, acute effects of marijuana may include, but are not limited to: intoxication (changed perceptions, thinking, memory, judgment, impaired driving or work or school performance for hours to days after last dose, risks for accidents, injuries, falls); psychological effects (anxiety, panic, paranoia, increased appetite); cardiovascular effects (increased heart rate, blood pressure, increased risk of heart attack, increased risk of stroke, injury to brain blood vessels) and worsening of symptoms of asthma, other lung conditions. The long term effects of smoking marijuana are associated with, may include, but are not limited to: addiction, withdrawal symptoms, problems with academics, work, social interactions; Impaired cognition (learning, memory, executive function, lowering of IQ); psychosis (schizophrenia other psychiatric disorders); bronchitis, asthma symptoms, heart attack, testicular cancer; unborn children may develop behavioral, developmental, cognitive impairment.

69. I am aware of no recent study with a large cohort of marijuana-naïve subjects that would compel the conclusion that there is an acceptable level of safety for use of marijuana under medical supervision. Without long-term studies and an assurance of consistent composition of the substance, and without proof that the substance is free of contamination or adulteration, one cannot conclude that there is an acceptable level of safety for marijuana's use under medical supervision. Marijuana's chemistry, manufacturing, and specifications must be further studied, developed, and chemical isolation

of its cannabinoids should be encouraged.

70. Simply put, further information about the safety and effectiveness of marijuana and its constituents is needed. Clinical trials of marijuana (and especially its isolated constituents) conducted under an IND application, and adequately powered (sufficiently large number of subjects) could collect this important information as a part of the drug development process.

71. Under these circumstances, exposing patients to the known negative side-effects of marijuana, particularly in smoked or other delivery forms, is being done without an adequate understanding (by the user or physicians) of the long-term negative effects. DEA, in conjunction with FDA, were well-justified in reaching the conclusion that the safety assurances required for medicines were lacking when they denied the most recent petition to reschedule marijuana in 2011. *See* Denial of Petition To Initiate Proceedings To Reschedule Marijuana, 76 F.R. 40552 (July 8, 2011).

72. Until reliable research into the long-term consequences of chronic marijuana for asserted medical conditions is conducted, it is too soon to know what users are being exposed to. Many potential users are vulnerable, uninformed about the lack of safety and safeguards, in a poor position to objectively judge and weigh the potential risks, and may harbor psychiatric conditions, cognitive impairment, motor incoordination, or latent cardiovascular disease that can be exacerbated by marijuana use. Thus, at this time, there is a strong basis for concluding that adequate safety assurances for the use of marijuana, even under medical supervision, are lacking.

VI. REBUTTAL TO OPINIONS OF THE DEFENSE EXPERTS

73. I have reviewed the declarations filed by the defense in this matter, and disagree with a number of the statements made therein. Below, I set forth specific points of disagreement and rebuttal, which I can expand upon if called to testify orally.

74. In general, the declarations offered by the defense are flawed because they ask the wrong question. There is anecdotal evidence that marijuana use by some people appears to make them feel better or to cope with their conditions, and very limited, quality clinical evidence. And, as stated above, there is promising medical research into some of the compounds found in marijuana. But this does not mean that marijuana should be available to the general public as medicine, nor that it has an accepted medical use. At a minimum, further reliable studies are required to test the efficacy and safety of marijuana.

A. Rebuttal to Declaration of Dr. Carter

75. Dr. Carter is incorrect in claiming that the chemistry of marijuana is well known and highly reproducible. While it is true that the chemical composition of smoked marijuana has been analyzed and is known in general terms (e.g., Moir et al, A Comparison of Mainstream and Sidestream Marijuana and Tobacco Cigarette Smoke Produced under Two Machine Smoking Conditions. *Chem. Res. Toxicol.*, 2008, *21* (2), pp 494–502), there is no standard "marijuana" chemistry. The chemical composition of marijuana depends on too many conditions, including soil quality, light quality, microbiological environment, water supply, mineral content of the soil, fertilizer and pesticide use, and other environmental factors which are not controlled or regulated. Moreover, marijuana growers have manipulated the germ seeds of marijuana to raise the THC content dramatically over the past decade and reduce CBD content (to increase the "high"). No assumptions can be made on the content of the other 80+ cannabinoids in the plant when the major constituents have been so significantly altered.

76. Dr. Carter also claims that adequate efficacy and safety studies exist for using marijuana as a medicine. It is my opinion that he is in error for the reasons stated above.

77. Dr. Carter's claim that a large body of randomized, double-blinded, placebo-controlled clinical trials documenting the efficacy of marijuana as treatment is incorrect. While there are a number of large, controlled double-blinded clinical trials with isolated cannabinoids, those for *smoked marijuana* are scarce. Smoked or ingested marijuana is not equivalent to oral or sprayed THC, CBD, Marinol, Nabilone, or any other combination of isolated cannabinoids. In addition, most of the early research on therapeutic benefit of marijuana is unacceptable by modern standards because these were survey, open or case studies, in which participants were not randomized to placebo or drug, nor blinded to whether they were receiving placebo or drug, but asked to self-report marijuana benefits. In carefully controlled clinical trials, subjects are randomly assigned to control or experimental groups (or crossed-over to the other group), other medications are either withdrawn or their doses are reported, and investigators make every effort to devise methods to objectively quantify outcomes. Without these methods, the results of such studies are of little scientific utility.

78. In addition, Dr. Carter's citation of 20,000 + peer-reviewed articles on marijuana benefits offers no support for his claim because many of these articles describe the *adverse*

consequences of marijuana use, the neurobiology of the endocannabinoids and their receptors, cannabinoid drug discovery, analytical methods, epidemiological and psychological studies, and others irrelevant to clinical trials.

79. Dr. Carter also cites to a paper by Dr. Nora Volkow for support of his opinion that marijuana has medical benefits. In reality, the point of Dr. Volkow's article is to voice concern that the spread of marijuana through the medical or legalization route is troublesome in view of the growing evidence of the *adverse* health effects of marijuana, including addiction, poor school performance, memory impairment, compromised lifetime achievement, relationship to mental illness, gateway drug effects, risks during brain development, risks of cancer, motor vehicle accidents, and other conditions set forth above. Dr. Volkow concludes, and I agree, that there is a need to improve our understanding of how to harness the potential medical benefits of the compounds within the marijuana plant without exposing people who are sick to its intrinsic risks. The same is true of the cited Institute of Medicine (IOM) report *Marijuana and Medicine*, which acknowledges the potential benefits of marijuana-derived compounds but stresses the importance of focusing research efforts on the therapeutic potential of synthetic or pharmaceutically pure cannabinoids, and states that there is no future in smoked marijuana. The IOM report emphasized that smoked marijuana is a crude drug delivery system that exposes patients to a significant number of harmful substances, and concludes that "if there is any future in marijuana as a medicine, it lies in its isolated components, the cannabinoids and their synthetic derivatives." There are particular concerns with regard to long-term smoking of marijuana by vulnerable populations, including some evidence to suggest that use of marijuana by patients with HIV/AIDS symptoms may actually exacerbate HIV-associated cognitive deficits.

80. Dr. Carter also claims that cannabis, if metabolized, will not become another controlled substance. This claim is without support. It is not possible to conclude this without knowing the content, metabolism and pharmacology of each of the 80+ cannabinoids in the marijuana plant, which is presently unknown.

81. Dr. Carter's opinions on the abuse potential for marijuana are also mistaken, and largely premised on avoiding a definition of abuse or addiction. As noted above, the DSM-IV and DSM-V criteria provide the appropriate definition, are founded on solid scientific evidence, and widely used by

psychiatrists, other physicians and treatment specialists to define abuse or addiction. In both the earlier and current version of DSM, and deliberated by a panel of experts in psychiatry, addiction treatment, and psychology, the evidence that marijuana is an abusable and addictive drug is abundant. Furthermore, comparisons with other drugs are immaterial to determining whether marijuana has a high abuse potential. First, each addictive drug can produce a unique set of adverse consequences, in addition to addiction. Second, the prevalence of addiction for early onset marijuana users is as high as other addictive drugs such as cocaine. Finally, the Institute of Medicine Report is now considered obsolete regarding its conclusion on "less severe, less likely" marijuana addiction. More recent studies and higher potency marijuana have altered this view considerably, and strongly support the views I have expressed above.

82. In addition, Dr. Carter claims that cannabis is widely used, but that its "negative consequences remain rare" and that THC-impaired driving is not a problem**.** This view is not sustainable, as evidence mounts on marijuana-associated driving fatalities (see references in earlier sections), amotivational syndrome, impairment of judgment, association with psychosis, reduction of IQ, cognitive and memory impairment, neurodevelopmental problems, and pulmonary and cardiovascular problems. (*See, e.g.*, Thomas G, Kloner RA, Rezkalla S. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: what cardiologists need to know. Am J Cardiol. 2014 Jan 1;113(1):187-90).

83. Dr. Carter's testimony about marijuana's use as a medicine is largely based on a paper submitted to DEA as an attachment to the pending petition to remove marijuana from Schedule I. Neither Dr. Carter's conclusions in his declaration, nor the conclusions of his paper, are well-founded. In brief, his conclusions largely rely on outdated information, studies of inadequate size or quality, or that conflate the medicinal value of compounds within marijuana, or synthetic cannabinoids, with marijuana itself. While there is growing evidence that isolated THC-CBD mixtures, CBD alone, other phytocannabinoids, and synthetic cannabinoids have promise as medicine, that does not make the marijuana plant (of unknown quality, composition, and side-effects) into medicine. If anything, it means that the traditional process of isolating and standardizing these compounds, now routine for other plant-based medications, will obviate the

disputes about the use of marijuana (and especially smoked marijuana) as medicine. For example, non-psychoactive cannabidiol, if proven effective in clinical trials for certain forms of epilepsy, will obviate this therapeutic claim for the intoxicating marijuana plant. There is, at present, insufficient support for the claim that the marijuana plant is medically effective or safe for use in treating these chronic conditions.

84. The data does not currently support the conclusion that the marijuana plant itself is an effective treatment. In neurological diseases, no reliable conclusions can be drawn (Koppel et al, 2014). For patients with Huntington's disease; for patients with Parkinson's disease, cannabinoids are probably ineffective for treating levodopa-induced dyskinesias; for patients with Tourette syndrome: data is insufficient to support or refute efficacy of THC for reducing tic severity; for patients with cervical dystonia: data is insufficient to support or refute the efficacy of dronabinol; for patients with epilepsy: data is insufficient to support or refute the efficacy of cannabinoids for reducing seizure frequency. Against this background, the risks and of using marijuana should be weighed carefully.

85. None of the research by the Center for Medicinal Cannabis Research ("CMCR") establishes a currently accepted medical use. CMCR was designed to coordinate rigorous scientific studies to assess the safety and efficacy of cannabis and cannabis compounds for treating medical conditions, and funded by the state of California more than a decade ago. The legislation called for a program overseeing medical research that was objective and of high quality, intended to "enhance understanding of the efficacy and adverse effects of marijuana as a pharmacological agent." CMCR's research focused on the potential medicinal benefits of cannabis for diseases and conditions as specified by the National Academy of Sciences, Institute of Medicine Report (1999) and by the Workshop on the Medical Utility of Marijuana, National Institutes of Health (1997). Despite a decade of work and millions of dollars in funding, only 5 of 41 publications (excluding abstracts) from the CMCR report the effects of smoked cannabis in patients for alleviating medical conditions. Four are in patients with neuropathic pain, and one is in patients with multiple sclerosis. Several large and critical studies were cancelled because of inability to recruit an adequate number of subjects. In addition, with a slight deviation in one study, all subjects were required to be

experienced marijuana smokers. Given the small and skewed sample sizes, these results cannot be translated to the general public. A San Diego Union Tribune article republished on CMCR's own web-page states that:

> While much more is known today about the medical effectiveness of the species cannabis sativa than in 1996, scientists maintain that they can't prove efficacy for many conditions that marijuana is routinely used to treat. It's often difficult to distinguish what's simply promising from what has peer-reviewed scientific legitimacy, researchers said.

B. Rebuttal to Declaration of Dr. Denney

86. Dr. Denney claims that "accepted and used medically to treat multiple serious medical conditions, marijuana has been safely used under medical supervision for nearly sixteen years in the State of California and elsewhere. Moreover, the safety and medical efficacy of cannabis far exceeds that of many other prescribed and over-the-counter (OTC) medications, in that it is less toxic, possesses a low abuse potential, and is incapable of causing lethal overdose." This statement contradicts critical, scientific findings made in the past decade, as set forth above. Moreover, Dr. Denney implies that the safety and efficacy of drugs can be determined solely on the basis of overdose deaths or physical side effects. This is incorrect. Accumulating evidence indicates that frequent marijuana use is associated with significant adverse brain and behavioral consequences, that can be more disruptive to normal life than side effects of, for example, antibiotics. In addition to acute intoxication with potential hazards to self and others, marijuana has abuse potential, is addictive and a robust marijuana withdrawal syndrome has been described by several authors and demonstrated in preclinical, clinical, and epidemiological studies. It is comparable to nicotine or cocaine withdrawal. Marijuana withdrawal is reported by up to one-third of regular users in the general population and by 50%–95% of heavy users in treatment or research studies. The clinical significance of marijuana withdrawal is demonstrated by use of marijuana or other substances to relieve it, its association with difficulty quitting, and worse treatment outcomes associated with greater withdrawal severity.

87. In addition, Dr. Denney is simply incorrect about marijuana's use under medical supervision. Marijuana differs significantly from normal, FDA-approved prescription medications, and evidence supporting its use as a medication is not consistent with the standards of the FDA's

current drug approval process. It is also often used in a manner that is inconsistent with standard practice of medicine that requires maintaining patient records, objectively determining cause of symptoms, follow-up care, and limiting repeat prescriptions, on a case-by-case determination. Marijuana is smoked, while other medications are not smoked. Its safe dose ranges (for THC? other cannabinoids? ammonia?), side-effects if taken as a medicine long term, acceptability for marijuana-naïve patients, long-term effects, and ability to engender tolerance or sensitization in marijuana-naïve or experienced smokers, are all unknown. And, as noted above, I am aware of no research on the critical question of marijuana's safety and effectiveness for use for medical conditions that span multiple years. Without this data, and without a consistent, pure, standard, and well-understood product, one cannot conclude that there are adequate assurances that marijuana can be safely used as a medicine by the general public, particularly when we know of its adverse consequences as summarized in the recent New England Journal of Medicine article by Volkow, et al., cited above.

88. Dr. Denney correctly points out that many over-the-counter drugs can be dangerous if taken in the wrong quantities. But this does not mean that marijuana is safe or even safer than these drugs.

89. The same is true for Dr. Denney's comparisons of over-the-counter medications, alcohol, and tobacco. The same psychological effects (relaxation, etc.) he reports for marijuana are also frequently reported for alcohol and tobacco products. But a diligent physician would not prescribe alcohol or smoking cigarettes for a patient. Moreover, there is no evidence that that any of the over-the-counter medications listed in his declaration produce a unique spectrum of negative side-effects of marijuana, such as learning and memory impairment, loss of judgment, distorted time perception, paranoia, addiction, cognitive deficits, IQ decreases, or significant brain changes, pulmonary deficits, or cardiovascular events. Moreover, and as noted above, a robust marijuana withdrawal syndrome has been described by several authors and demonstrated in preclinical, clinical, and epidemiological studies. It is comparable to nicotine withdrawal. Marijuana withdrawal is reported by up to one-third of regular users in the general population and by 50%–95% of heavy users in treatment or research studies. The clinical significance of marijuana withdrawal is demonstrated by use of marijuana or other substances to relieve it, its association with difficulty quitting, and worse treatment outcomes associated with greater withdrawal severity.

90. Dr. Denney is incorrect to downplay the association between psychosis and cannabis use. Association-based case-studies, surveys, and epidemiological studies indicate a strong association between marijuana and psychosis or psychotic disorders, including schizophrenia. Symptoms of schizophrenia increase with marijuana use, and the magnitude of the symptoms is associated with amount used and frequency of use. In individuals with an established psychotic disorder, cannabinoids can exacerbate symptoms, trigger relapse, and have negative consequences on the course of the illness. At the present time, the evidence indicates that marijuana may be a component cause in the emergence of psychosis, and further research is continuing. (*See, e.g.*, Radhakrishnan R, Wilkinson ST, D'Souza DC, *Gone to Pot - A Review of the Association between Cannabis and Psychosis*, Front Psychiatry. 2014 May 22;5:54; Degenhardt et al 2013).

91. Dr. Denney's declaration that he has "found cannabis has been successfully used to treat psychological disorders such as anxiety, depression and PTSD in a number of patients who have not found other treatments sufficiently helpful" does not establish that marijuana has a currently accepted medical use for the general public. Furthermore, as quoted above, the American Psychiatric Association's position (December 2013) is that that: "There is no current scientific evidence that marijuana is in any way beneficial for the treatment of any psychiatric disorder. In contrast, current evidence supports, at minimum, a strong association of cannabis use with the onset of psychiatric disorders. Adolescents are particularly vulnerable to harm, given the effects of cannabis on neurological development." There are no objective randomized control trials that demonstrate cannabis effectiveness has been successfully used to treat psychological disorders such as anxiety, depression and PTSD (e.g. Greer et al 2014). Marijuana is not a medically approved method to treat these disorders.

92. Dr. Denney's citation to a survey conducted by the *New England Journal of Medicine* in 2013 for the proposition that the majority of clinicians favored of the use of marijuana for medicinal purposes is misleading. The article cited a case of a terminally ill cancer patient, which is not at all typical of patients requesting a recommendation for marijuana (Adler JN, Colbert JA. *Clinical decisions, Medicinal use of marijuana--polling results*, N Engl J Med. 2013 May 0;368(22):e30). As such, it generated much debate, support and refutation by others, who highlighted

the unusual and morbidly ill patient with metastatic breast cancer in this presentation (Bostwick JM, Reisfield GM, DuPont RL. *Clinical decision, Medicinal use of marijuana*. N Engl J Med. 2013 Feb 28;368(9):866-8). As Dr. Bostwick, et al., explained, there is no benefit to smoking marijuana, though likely little risk to such an advanced cancer patient. Moreover, they explain that

> Smoked marijuana is a nonmedical, nonspecific, and potentially hazardous method of drug delivery. The cannabis plant contains hundreds of pharmacologically active compounds, most of which have not been well characterized. Each dispensed quantity of marijuana is of uncertain provenance and of variable and uncertain potency and may contain unknown contaminants. There are other questions to consider in Marilyn's case. Could marijuana's cognitive side effects, particularly its effects on memory, promote or exacerbate chemotherapy-induced cognitive dysfunction? If Marilyn's pulmonary disease includes lymphangitic spread, could smoking cause hypoxemia? What effects will marijuana's potential immunologic hazards (e.g., chemical constituents, pyrolized gases, viable fungal spores, or pesticide residues) have on her health during periods of immunocompromise? How will marijuana, alone or in combination with other medications associated with potential cognitive and psychomotor impairment, affect her ability to safely operate a motor vehicle? What are the possible effects of marijuana on tumor progression?

I agree with them that there are too many open questions to sanction the use of marijuana as medicine.

93. In addition, Dr. Denney's reliance on CMCR is inadequate for the reasons stated above, except to refute his own claim that marijuana research has been impaired. CMCR is well-funded and gained approval to conduct a number of clinical trials with marijuana for serious medical conditions, but was compelled to cancel five major studies due to lack of volunteers.

94. Dr. Denney also points to the use of THC and CBD as medicine to treat seizures and other conditions. He has inadvertently refuted his central claim: that marijuana is medicine. In reality, THC and CBD, isolated and administered at known doses, are approved as medicine. The marijuana plant, which contains CBD, THC, and 400+ other chemicals, is not. Modern medicine is based on pure compounds, known doses, known benefits and side effects and long term outcomes. Conflating marijuana with isolated cannabinoids misunderstands the scientific literature, and confuses physicians, policy makers and patients. In the 21st century, patients deserve evidence-based medicines that are safe, effective, and of known composition for proven indications.

C. Rebuttal to Declaration of Carl Hart.

95. I also disagree with the conclusions of Carl Hart for the reasons already set forth above, and thus will not restate those same reasons here.

VII. CONCLUSION

96. There is a strong scientific foundation for continuing to include marijuana on Schedule I of the Controlled Substances Act. There was strong support for DEA's prior decisions, including in 2001 and 2011, and the evidence remains strong today. Nothing in the scientific record compels the conclusion that marijuana can no longer be on Schedule I.

I swear that the foregoing is true and correct to the best of my knowledge. Executed this 29th day of July, 2014, at Belmont, Massachusetts.

By:

Bertha Madras, Ph.D