

The DEA's Denial of Existing Medical Cannabis Research

A Peer-Reviewed Comparative Analysis of DEA's
"Denial of Petition to Initiate Proceedings to Reschedule Marijuana"

Prepared by Americans for Safe Access (2016)

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Publication date July 2016 With over 100,000 active members in all 50 states, Americans for Safe Access (ASA) is the largest national member-based organization of patients, medical professionals, scientists and concerned citizens promoting safe and legal access to cannabis for therapeutic use and research. ASA works to overcome political and legal barriers by creating policies that improve access to medical cannabis for patients and researchers through legislation, education, litigation, grassroots actions, advocacy and services for patients and their caregivers, the medical cannabis industry, and governments.

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Table of Contents

I.	Foreword	4
II.	Introduction.....	5
III.	Common Ground	6
	Factor 1b: There is no significant diversion of the substance from legitimate drug channels.....	6
	Factor 1d: Cannabis is related to other approved drugs with acceptable safety profiles.	7
	Factor 6: That the “gateway” hypothesis is not supported by scientific evidence.	7
	Factor 8: Cannabis is not an immediate precursor to a controlled substance.....	8
IV.	Comparative Analysis of Available Data vs HHS Report.....	8
V.	Evaluating the DEA's Rationale for 1) Marijuana has a high potential for abuse.....	11
	DEA's Evidence.....	11
	Available Scientific Data.....	12
VI.	Evaluating the DEA's Statement 2) Marijuana has no currently accepted medical use in treatment in the Unites States... 12	
	Element (1) The drug's chemistry is known and reproducible.	13
	DEA/FDA Evidence for Element 1	13
	Available Scientific Data for Element 1	14
	Element (2) There are adequate safety studies.....	17
	DEA/FDA Evidence for Element 2	18
	Available Scientific Data for Element 2	18
	Element (3) There are adequate and well-controlled studies proving efficacy.....	19
	DEA/FDA Evidence for Element 3	19
	Available Scientific Data for Element 3	19
	Element (4) The drug is accepted by qualified experts.	20
	DEA/FDA Evidence for Element 4	20
	Available Scientific Data for Element 4	20
	Element (5) The scientific evidence is widely available.....	23
	DEA/FDA Evidence for Element 5	23
	Available Scientific Data for Element 5	23
VII.	Evaluating the DEA's Statement 3) Marijuana lacks accepted safety for use under medical supervision.	24
	DEA's Evidence Regarding Safety	24
	Available Scientific Data Regarding Safety	24
VIII.	Conclusion.....	25
	Recommendations	25

I. Foreword

Today over 300 million Americans live in states with medical cannabis laws, and over 2 million individuals are legally using medical cannabis under these state programs. However, all of these patients and programs are in violation of federal laws. According to the Department of Justice (DOJ), this is due to the fact that Congress determined that cannabis belongs in Schedule I of the Controlled Substances Act (CSA).

However, the scheduling of cannabis has been a political – rather than scientific – establishment from the very beginning. In 1970, cannabis was placed in Schedule I under the CSA as a placeholder, pending evaluation by a government-appointed commission known as the National Commission on Marihuana and Drug Abuse – since known as the Shafer Commission after the Commission's chairman, Raymond P. Shafer. Even though the Shafer Commission recommended decriminalization of cannabis and medical availability, these policies were rejected by President Nixon *before* the report could be published. Despite numerous advances in science and research in the medical value of cannabis, due to political forces, as well as Drug Enforcement Administration (DEA) and U.S. Food and Drug Administration (FDA) policies that were designed for prescription drugs, cannabis has been stuck in Schedule I ever since.

Under these circumstances, the current rescheduling process will never allow cannabis to be rescheduled. This is made clear in the DEA's most recent "*Denial of Petition to Initiate Proceedings to Reschedule Marijuana*," which focuses on the fact that cannabis does not fit with current federal regulations for a FDA approved drug, i.e. the medical value assigned to cannabis does not meet their definition of "medicine," not that cannabis has no medical value.

This is the 4th time in just over 4 decades that the DEA has denied a petition to reschedule cannabis. Not only has the DEA taken several years to respond to each petition, but special rules for cannabis are created and applied whenever there is data that does not support their policy. In the 1990s, the DEA established a "5-element test" to determine if there was accepted medical use for a drug. However, the consequences of not satisfying this test to fulfil the DEA's definition of medicine have only been applied to cannabis. Applying prescription drug standards – such as those required for FDA approval – to a botanical drug is a case in point of special rules being applied where they wouldn't be otherwise. Rather than using the FDA guidelines for botanical drugs, cannabis is criticized as though it were a purified pharmaceutical agent, and not a botanical medicine.

The rescheduling process has been designed for prescription drugs to move between the schedules, and not for a Schedule I substance to enter into less restrictive schedules. This unworkable process for botanical medicines, including but not limited to cannabis, has led 42 states plus the District of Columbia to create their own definitions of medicine and distribution.

The DEA's recent decision shows that the war against medical cannabis will unfortunately continue unabated, and unaffected by either reason or scientific evidence. Until these policies can be changed, the only viable solutions will require action by Congress.

II. Introduction

In April 2011, the Department of Justice (DOJ) sent letters to governors of 9 medical cannabis states “clarifying” that medical cannabis programs – and specifically regulated distribution programs – were in violation of federal law, due to the Schedule I status of marijuana. In response, in November of the same year, Governors Lincoln D. Chafee (RI) and Christine O. Gregoire (WA), petitioned the DEA to initiate rulemaking proceedings under the rescheduling provisions of the CSA – to remove marijuana and “related items” from Schedule I of the CSA and to reschedule as “medical cannabis” in Schedule II. After nearly five years of review, on August 10, 2016 the DEA responded to the petition with a document entitled *Denial of Petition to Initiate Proceedings to Reschedule Marijuana* (herein referred to as the “DEA report”).

The DEA concluded that “marijuana” (cannabis) should not be removed from the Schedule I status due to the below 3 factors:

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

DEA chief Chuck Rosenberg stated that this decision was based heavily on the FDA’s determination if marijuana is “a safe and effective medicine.” This determination was based upon input from the Department of Health and Human Services (HHS), which was conducted in consultation with the National Institute on Drug Abuse (NIDA).

The DEA report cited the following in making their determination:

1. U.S. Department of Health and Human Services (HHS) – Basis for the Recommendation for Maintaining Marijuana in Schedule I of the Controlled Substances Act (page 7).
2. While not listed in their cover letter as a submitted document, a review article added at the end of the bibliography of the HHS report, entitled *The Medical Application of Marijuana: A Review of Published Clinical Studies* prepared by the U.S. Food and Drug Administration (page 66).
3. U.S. Department of Justice - Drug Enforcement Administration (DEA), Schedule of Controlled Substances: Maintaining Marijuana in Schedule I of the Controlled Substances Act, Background, Data, and Analysis: Eight Factors Determinative of Control and Findings Pursuant to 21 U.S.C. 812(b) (Page 115).

While we do not agree with the DEA’s final determination that marijuana is not a safe and effective medicine, we do appreciate the time and resources the DEA put into making this decision. We are pleased to see a few areas of agreement between their report and the available scientific data on cannabis. Generally, our analysis found that the DEA admits that cannabis satisfies several criteria regarding the 8-Factor analysis.

However, the DEA report included both inaccurate and unclear background materials pertaining to the scheduling process of cannabis, conjoined to misinterpretations of the CSA in general. In one clear

example of this, the report states there are *no known* standardized cannabis products. The DEA chose to use a misinterpretation of the CSA to exclude any clinical research conducted with standardized cannabis extracts from the HHS report. The report defines cannabis/marijuana in the CSA as including derivatives and extracts of cannabis/marijuana such as purified THC, CBD, and nabiximols. However, in the DEA's *political* view, these resinous hash oils do not count as standardized cannabis products, nor do the cannabis cigarettes that NIDA themselves produce according to DEA (and FDA) guidelines and mandate. Clinical studies with resinous hash oil extractions were systematically excluded in the DEA's denial of rescheduling report.

Actual standardized "cannabis medicines" include purified THC, purified CBD, THC/CBD mixtures, and nabiximols (commonly known as Sativex®). Purified CBD and Sativex® are FDA approved under IND for pediatric epilepsy, and in Phase III clinical trials in the U.S., respectively. Marinol® is an FDA approved cannabis product known as dronabinol. There exists no evidence of significant abuse, nor black market or diversion issues, with currently available standardized medicinal cannabis products – including dronabinol, nabiximols, or NIDA's cannabis products. Such persistent misinterpretation of existing law – coupled to apparent lack of knowledge of prevailing scientific investigations concerning both general safety and medicinal usefulness – suggests that an uninformed and unbalanced opinion of cannabinoid-based medicine is being advanced.

In anticipation of the DEA's pending decision on the scheduling of medical cannabis, Americans for Safe Access (ASA) coordinated world experts on cannabis to draft an independent [8-Factor Analysis](#) based on all available data that concluded that cannabis does not meet the requirements for a Schedule I substance under the CSA. The following memo is a comparative analysis of the research and findings used by the DEA to make their determination that cannabis remain a Schedule I drug. The references in this memo refer to DEA materials and ASA's 8-Factor analysis.

III. Common Ground

The DEA report claims that cannabis satisfies some sections of the 8-factor analysis. This means there are sections where we all agree that cannabis meets the criteria for rescheduling. In short, we agree with the DEA that cannabis satisfies Factors 1b, 1d, 2, 3, 6, and 8 (of the 8-factor analysis). For example, the DEA cites research demonstrating that there is no evidence for long term harms associated from the chronic use of cannabis to satisfy Factors 2 and 3.

Below are the Factors and the statements from the DEA to which we agree regarding cannabis as a medicine and its rescheduling.

Factor 1b: There is no significant diversion of the substance from legitimate drug channels.

Factor 1b definition: *"There is significant diversion of the substance from legitimate drug channels."*

On page 11, the DEA states, *"There is a lack of evidence of significant diversion of marijuana from legitimate drug channels."*

We agree with the FDA and DEA that legal cannabis products have not suffered from significant diversion and additionally that cannabis is not a precursor for another schedule drug. Pure THC has been FDA approved since the 1980s and no significant black market for Marinol is known to exist.

Factor 1d: Cannabis is related to other approved drugs with acceptable safety profiles.

Factor 1d definition: *"The substance is not 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 it is not 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."*

On page 12 the DEA states, *"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."* Furthermore, the DEA goes on, *"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 Marional [sic] 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."*

We agree with the DEA and FDA that *cannabis* is a substance related in action to Marinol and Cesamet. THC (marinol) and Cesamet are two FDA approved drugs with acceptable safety profiles (i.e., low abuse potential) and no evidence of any significant diversion. Factors 2 and 3: Scientific Evidence for the Pharmacological Effects and the State of Current Scientific Knowledge Regarding the Drug or Other Substance.

On page 12, the DEA report states, *"Abundant scientific data are available on the neurochemistry, toxicology, and pharmacology of marijuana."*

On page 20, the DEA report states, *"cannabis-associated cognitive deficits are reversible and related to recent cannabis exposure, rather than irreversible and related to lifetime use."*

On page 22, the DEA report states, *"At present, the available data do not suggest a causative link between marijuana use and the development of psychosis."*

We agree with the DEA that the effects of cannabis are non-toxic and have no long-term consequences on the human brain. Available data show that the chemistry of cannabis is well understood and does not cause significant harm to the adult brain.

Factor 6: That the "gateway" hypothesis is not supported by scientific evidence.

Factor 6 definition: *"What, if any, risk there is to public health."*

On page 43, the DEA report states, *"Overall, research does not support a direct causal relationship between regular marijuana use and other illicit drug use."*

On page 44, the DEA report states, *"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."*

On page 162, the DEA report states, *"The HHS reviewed the clinical studies evaluating the gateway hypothesis in marijuana and found them to be limited."* The DEA goes on to say, *"The HHS cited several studies where marijuana use did not lead to other illicit drug use."*

On page 162, the DEA report states, *"Based on these studies among others, the HHS concluded that although many individuals with a drug abuse disorder may have used marijuana as one of their first illicit drugs, this does not mean that individuals initiated with marijuana inherently will go on to become regular users of other illicit drugs."*

Over 40 years ago the "gateway" hypothesis of cannabis was proposed. The report concludes predictably, that the gateway theory of cannabis is not supported by the evidence. We agree that the hypothesis attempted but failed to predict that cannabis use leads to the addiction of other drugs. Furthermore, no clinically significant adverse public health effects related to rescheduling cannabis were provided to by the DEA.

Factor 8: Cannabis is not an immediate precursor to a controlled substance.

Factor 8 definition: *"Whether the substance is immediate precursor of a substance already controlled under the article."*

On page 46, the DEA report states, *"Marijuana is not an immediate precursor of another controlled substance."*

We agree that cannabis is not an immediate precursor of another controlled substance.

While not sufficient for the DEA to reschedule, these statements show an evolution in the DEA's opinions on cannabis. All federal conversations about cannabis should begin with the above information.

IV. Comparative Analysis of Available Data vs HHS Report

The 2016 HHS evaluation and the additional data gathered by the DEA constitute a document, entitled "Basis for the Recommendation for Maintaining Marijuana in Schedule I of the Controlled Substances Act." This document supporting the basis of the DEA recommendation was preliminarily scrutinized by ASA through use of a comparative reference analysis, in which we categorized and characterized each reference in the DEA's basis article according to multiple criteria (each references can have more than one category selected). Our goal in doing this was to compare the *proportion* and *type* of research article utilized in forming the DEA decision with that of the current available data that ASA used to write their 8-Factor Analysis.

Criteria/categories are as follows:

- Peer Reviewed (Peer reviewed research articles of any type)

- Non-Peer Reviewed (Agency and policy documents, journalistic pieces, no independent 3rd party analysis)
- Clinical Research (Clinical research with controlled dosing looking for therapeutic effect)
- Safety Studies (may or may not have controlled dosing, not investigating therapeutic effects but safety)
- Animal (Animal based research, rats, mice and their brains)
- Surveys (Sociology and epidemiology research, survey based research articles)
- Human Brain (Research pertaining to the human brain, disease, and toxicology to neuronal tissue)
- Reviews (Review type article and reference manuals)
- Original Publication (Original research article cited, opposite of review article)
- <2000 (published during the year 2000 or earlier)
- >2001 (Published in the year 2001 or later)
- Product Safety Related (Research on medical cannabis programs, product safety, traffic and fatality research in states with medical cannabis programs)

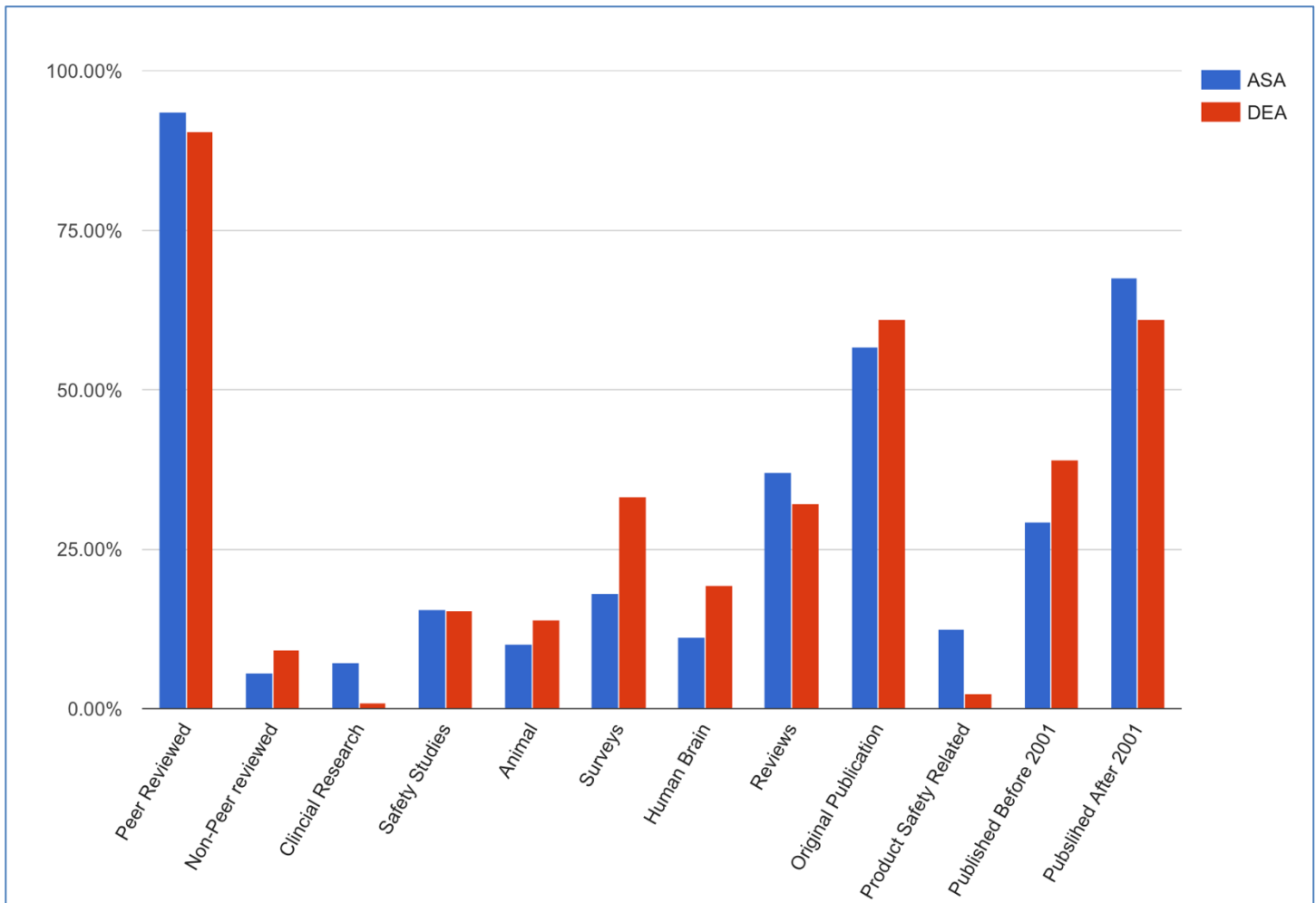


FIGURE 1 PROPORTION AND TYPE OF REFERENCES USED IN REPORTING

Table 1. Number, Type and Percentage of Citations Used

	ASA (558 Citations)		HHS Report (207 Citations)	
Title	Proportion of Research Meeting Criteria	Number of Citations	Proportion of Research Meeting Criteria	Number of Citations
Peer Reviewed	93.55%	522	90.38%	188
Non-Peer reviewed	5.56%	31	9.13%	19
Clinical Research	7.17%	40	0.96%	2
Safety Studies	15.59%	87	15.38%	32
Animal	10.04%	56	13.94%	29
Surveys	18.10%	101	33.17%	69
Human Brain	11.11%	62	19.23%	40
Reviews	36.92%	206	32.21%	67
Original Publication	56.63%	315	61.06%	127
<2000	29.21%	163	38.94%	81
>2001	67.56%	377	61.06%	127
Product Safety Related	12.54%	70	2.40%	5

Data was generated by adding together all qualifying studies listed in each criterion, then dividing the total number of articles to generate a percentage or proportion.

In comparison, ASA's 8-Factor analysis utilized a significantly higher proportion and number of clinical research references and product safety related publications in its determinations. The DEA devoted less than 1% of their referenced work to addressing clinical cannabinoid trials, and consists of almost 10% non-peer reviewed publications, as compared to ASA's 5%.

Fully, one-third of the DEA's report is based only on surveys, regarding sociology and epidemiology. These types of studies largely lack any clear clinical applications or scientific relevance. For example, the DEA repeatedly cites surveys about cannabis use and suggested associations with psychosis, while completely disregarding clinical correlations such as research from the last 10 years demonstrating that suicide risks are not significantly increased with use.

The discrepancy between pre- and post-2001 literature in the analysis requires additional emphasis. Almost 40% of the DEA report relies primarily on outdated research articles, many of which have not been reproduced by the scientific community. In contrast, the ASA 8-Factor analysis uses almost 70% of research citations that have been published within this century, conducted with modern scientific instrumentation and controls. Several of the research articles used in the DEA report are so dated, that they do not provide any practical information to address current issues. Research studies primarily

published in the last 15 years, focus more on clinical studies using standardized cannabis products and biomedical breakthroughs in multiple sclerosis, cancer, regenerative and personalized medicine.

Pertaining to safety, the DEA report does not include any research regarding more recent standards of safety. For instance, there is no mention of the volume of product safety research that exists on cannabis and botanical medicine regulations today. Nor does it mention any relevant medical cannabis research on edible products from John Hopkins University, which was prominently published in the Journal of the American Medical Association (JAMA) and covered by well over 200 media outlets upon its publication. The DEA report also ignores the *book* on the quality control and quality assurances of medical cannabis products published by the Research Triangle Institute (RTI).

This analysis provides a characterization of the DEA's basis report.

In summation:

- DEA's basis report had only 207 citations, as compared to ASA's 558.
- ASA's report was submitted for peer-review to external third parties; there is *no evidence* that the DEA basis report was peer reviewed, there are *no listed authors*, and thus *no accountability* at the either the FDA, DEA, or HHS.
- DEA's basis report is deficient in addressing clinically relevant harms associated with cannabis.
- DEA's basis report is deficient in addressing clinical trials with existing standardized cannabis-based medicines (2 citations; representing <1% of the citations).
- Nearly 1/10th of the DEA basis report comes from non-peer reviewed sources.
- Fully 1/3rd of the DEA's basis comes from epidemiologic and survey based research, many of which do not bare clinical significance or do not demonstrate long term harm.
- The DEA's report was deficient in its analysis and reporting of medical cannabis products, i.e., 9,000 patient/years of placebo-controlled clinical research with nabiximols (i.e., cannabis extracts) was not even mentioned.
- While the DEA devoted a higher proportion of citations to the human brain (19%), it represents only 40 citations. While ASA cited 62 studies on the subject, which represents about 11% of ASA's 558 citations.

V. Evaluating the DEA's Rationale for 1) Marijuana has a high potential for abuse.

DEA's Evidence

"The HHS evaluation and the additional data gathered by the DEA show that marijuana has a high potential for abuse."

Available Scientific Data¹

If medical cannabis and related products had a high potential for abuse, there would exist a significant black market for both FDA and non-FDA approved medical cannabis products, such as FDA approved Marinol (pure THC), and the IND approved cannabis products Sativex®, Epidiolex®, and NIDA's catalogue of cannabis products for research (i.e., cannabis cigarettes). However, despite decades of availability, there is virtually no identifiable black market for NIDA's cannabis products, FDA approved Marinol, or the cannabis extracts Epidiolex and Sativex.

Marinol is pure THC, and can legally be created as a generic drug from the THC isolated from cannabis plants. Epidiolex and Sativex are standardized resinous extracts from cannabis plants. According to GW Pharmaceuticals' website and their widely available peer-reviewed clinical publications, their cannabis extract Sativex has already been utilized in Phase II and III clinical trials in the U.S. for almost 10 years, and without any abuse or diversion. Furthermore, biochemical fingerprinting of this standardized cannabis extract has been adequate for FDA CMC (Chemistry, Manufacturing, and Control) approval.

Another cannabis extract, marketed under the name Epidiolex, is part of a national clinical study in the U.S., investigating the role of this standardized product as frontline treatment in pediatric epilepsy. The University of Mississippi has been producing whole plant cannabis products for decades, and shipping about 300 cannabis cigarettes a month to IND patients since 1970, yet no report exists of finding these on the black market. GW Pharmaceuticals has produced more tonnage of cannabis than any other organization, legal or illegal, yet their cannabis extracts are simply *not found* on the black market. There exists no case whereupon either a user or abuser has arrived to a clinic for treatment of addiction related to the abuse of NIDA cannabis cigarettes, despite decades of use by IND patients. Further, neither Europe nor the UK have reported any significant development of a black market for medical cannabis products such as Sativex, Marinol, or pharmaceutical grade cannabis produced by Bedrocan®.

The DEA provides substantial evidence from surveys, that a great number of people report having used cannabis at some point within the last year. However, these surveys cited by the HHS report do not point to any relevant or significant negative public health outcome from these patterns of mass use. Indeed, cannabis is physiologically non-toxic (there is no known LD₅₀ for cannabis) and is not associated with causing any long-term negative health consequences.

VI. Evaluating the DEA's Statement 2) Marijuana has no currently accepted medical use in treatment in the United States.

"Based on the established five-part test for making such determination, marijuana has no currently accepted medical use," because:

¹ For Available Scientific Data references (i.e., [553]) please refer to the bibliography of ASA's peer reviewed 8-Factor analysis, available at: http://www.safeaccessnow.org/8_factor_analysis_on_cannabis.

“As detailed in the HHS evaluation, the drug’s chemistry is not known and reproducible; there are no adequate safety studies; there are no adequate and well-controlled studies proving efficacy; the drug is not accepted by qualified experts; and the scientific evidence is not widely available...This five-element test, which the HHS and DEA have utilized in all such analyses for more than two decades, has been upheld by the Court of Appeals. ACT, 15 F.3d at 1135.”

- Drug Enforcement Administration, August 12, 2016, Denial of Petition to Initiate Proceedings to Reschedule Marijuana

The above statement from the DEA defines that a drug has a "currently accepted medical use" if all of the following five elements have been satisfied:

1. the drug's chemistry is known and reproducible;
2. there are adequate safety studies;
3. there are adequate and well-controlled studies proving efficacy;
4. the drug is accepted by qualified experts; and
5. the scientific evidence is widely available.

In the absence of a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) approval, DEA has established a “five-element test” for determining whether the drug has a currently accepted medical use in treatment in the United States. Under this test, a drug will be considered to have a currently accepted medical use only if all five elements are satisfied.

The following are intact and unaltered quotes from the FDA’s submitted report regarding cannabis and the five elements. While FDA maintains that cannabis does not meet the 5-element test, we think the evidence points to the contrary.

Element (1) The drug's chemistry is known and reproducible.

Definition: “The substance’s chemistry must be scientifically established to permit it to be reproduced into dosages which can be standardized. The listing of the substance in a current edition of one of the official compendia, as defined by section 201(j) of the Food, Drug and Cosmetic Act, 21 U.S.C. 321(j), is sufficient generally to meet this requirement.” 57 Fed. Reg. 10499, 10506 (March 26, 1992).

DEA/FDA Evidence for Element 1

“Marijuana, as defined in the petition, includes all Cannabis strains. (For purposes of the CSA, marijuana includes all species of the genus Cannabis, including all strains therein). Based on the definition of marijuana in the petition, the chemistry of marijuana is not reproducible such that a standardized dose can be created. Chemical constituents including Δ^9 -THC and other cannabinoids vary significantly in marijuana samples derived from different strains (Appendino et al., 2011). As a result, there will be significant differences in safety, biological, pharmacological, and toxicological parameters amongst the various marijuana samples. Due to the variation of the chemical composition in marijuana samples, it is not possible to reproduce a standardized dose when considering all strains together. The HHS does advise that if a specific Cannabis

strain is cultivated and processed under controlled conditions, the plant chemistry may be consistent enough to derive reproducible and standardized doses."

Available Scientific Data for Element 1

There are two blatant issues with the DEA's statement on element 1. First, "strains," as listed by the DEA report, is not a technical or botanical term, it is a vague term and not appropriate. The terms that are appropriate to use are *chemovar* or *chemotype* (i.e., chemical variety). A chemovar is often defined as a particular species of plants, the chemical composition of which varies from the average because of different environmental growing conditions.

Second, the DEA report states above, "*Due to the variation of the chemical composition in marijuana samples, it is not possible to reproduce a standardized dose when considering all strains together.*" This statement is scientifically indefensible. No product or company is responsible for the scientific, nor manufacturing shortcomings of their predecessors. The fact that confiscated drug samples vary widely in potency across the nation, should bear no weight when discussing the products produced by licensed and pharmaceutical manufacturers. The DEA is implying that cannabis cannot be standardized based solely on data from their confiscated drug samples, which of course are not uniform in content. Illicit street cannabis varies widely in content but this has no relevance to developing standardized medical products and again it must be stressed that this is a scientifically indefensible statement from DEA.

The chemistry of cannabis is both known and reproducible. Complete cannabis monographs have been published, including one by the *American Herbal Pharmacopoeia* (AHP), setting clear, peer-reviewed guidance for standards of identity, analysis, quality control, administration, and dosing of cannabinoid-based medicine. The AHP monographs themselves are based on FDA and the United States Pharmacopeia (USP) guidelines for all botanical medicines. Additionally, standardized cannabis products are available from the NIDA-funded University of Mississippi marijuana farm for the FDA's IND program – a program that has provided standardized cannabis cigarettes to the same participants, every month, for decades. Furthermore, the Research Triangle Institute (A NIDA-funded, DEA-compliant organization) has also released a quality control manual for cannabis, entitled *The Analytical Chemistry of Cannabis – Quality Assessment, Assurance, and Regulation of Medicinal Marijuana and Cannabinoid Preparations*.

Internationally, private companies have completed controlled clinical studies and successfully marketed standardized cannabis products (flowers, extracts, and nabiximols) in 27 countries. In the last decade, the U.S. has approved over 550 studies of marijuana or cannabis, 144 with dronabinol or tetrahydrocannabinol (THC), and 96 with pure CBD or a CBD-rich cannabis extract, according to clinicaltrials.gov.

While cannabis is dispensed in pharmacies throughout Europe and at state-regulated dispensaries in the U.S., many conform to standards that would qualify cannabis products as botanical medicines, based on existing safety guidelines from the FDA, AHP, and the U.S. Department of Agriculture (USDA). The quality and safety of medical cannabis and its derivatives are adequately addressed by extant national and local standards. These standards also address best-practices for cannabis operations – such as manufacturers, cultivation sites, laboratories, and dispensaries.

Botanical medicines and herbal products *are* regulated. A diverse set of local, national and international botanical safety standards are directly applied to medical cannabis and cannabis products. Several

countries have made significant regulatory efforts to enact the existing national and local level standards for cannabis production and distribution [57,214,543]. Various countries have published monographs (i.e., Czech Republic, Holland, U.S., and Canada) to specifically address quality control of cannabis, including methodology. Trade associations, internationally, have published best practices for cultivation, dispensing, manufacturing, and laboratory practices [544]. Furthermore, an abundance of national and international guidance documents provide quality control standards that address nearly every aspect of quality control and product safety for botanical substances, such as cannabis and its derivatives.

One hurdle to quality control of medical cannabis products is the existing control status of cannabis in countries such as the U.S., as well as controls under the conventions. National and international controls prevent adequate product testing in U.S. cannabis programs, and may therefore inadvertently jeopardize public health. To date, there has only been a *single* study that examined labeling accuracy (i.e., potency) of those cannabis products' accessed through three state programs in the U.S. – A study that demonstrated that medical cannabis product labels can be inaccurate [545]. However, this U.S. study also demonstrated that the current national controls for cannabis serve to impair the ability to address public health concerns concerning medical cannabis and its derivatives.

It is difficult to address public health issues regarding medical cannabis products while it remains in Schedule I status. As the DEA tightly controls the release of analytical-quality standards for calibrating scientific instruments, cannabinoid compounds can only be purchased in necessary amounts if the operation has received a Schedule I license from the DEA. However, the DEA will not grant a Schedule I license to a state sponsored medical cannabis laboratory, because the laboratory would receive medical cannabis samples for analysis from non-DEA licensed sources (such as state licensed manufacturers, distribution centers, cultivation sites, patients, or doctors that recommend cannabis to patients). Therefore, the Schedule I status of Cannabis blocks most laboratories from determining the precise potency of a product. In contrast, testing for clinically relevant contaminants – such as heavy metals, bacteria, and fungus – can proceed without requiring DEA licensure, but this product safety testing is just as vulnerable to DEA or federal interference due to the scheduling status.

A potential normalizing factor for a medicine like cannabis in the U.S. could be for the USP to create a cannabis monograph; these standards could then be adopted to regulate cannabis as a medicinal product nationally [546]. However, such an action would grant pharmacists in the U.S. the ability to work with cannabis, which is forbidden by the DEA. Hence, the USP cannot create a cannabis monograph and still maintain compliance with the DEA. Presently, the USP defers to the AHP monograph as the current standard for cannabis products in the U.S. [7]. A recent meeting of the USP suggested that drafting of the document will not begin until cannabis is rescheduled – at least to a status that recognizes its medicinal use and outstanding safety profile. This lack of a permitted monograph (i.e., from the USP) is one of the issues that is directly responsible for the horrendous dereliction of responsibility in the industry to produce well-characterized, non-toxic products. A terrible public health threat has resulted from this policy. The best illustration is the pesticide contamination of legal cannabis in the Washington State market, that many patients now have no option but to utilize.

The standards issued by the AHP monograph and American Herbal Products Association (AHPA) have been adopted by 16 U.S. states to regulate product safety for their respective medical cannabis programs. Furthermore, AHPA – the trade association for the herbal products industry – has issued its medical cannabis manufacturing guidelines, completing its series of recommendations for state regulators in the areas of manufacturing, packaging and labeling, cultivation, dispensary operations, and laboratory

practices. Another example of medicinal cannabinoid production with outstanding quality assurances/controls exists in the Dutch program for medicinal cannabis. Produced under responsibility of the Ministry of Health, the program meets a number of quality requirements including, but not limited to: consistent strength on THC and composition of secondary cannabinoids, absence of microbiological contamination, pesticides and heavy metals, and humidity. Where there is a norm provided in the European Pharmacopoeia, this norm is followed [547].

The next sections below briefly discuss published resources and guidance documents being utilized by world governments to provide proper quality control and product safety for agricultural products and botanical medicines, including cannabis.

Good Agricultural and Collection Practices

The quality of raw material for botanical medicine can be safeguarded by using Good Agricultural and Collection Practices (GACP, aka GAP) to the extent possible in all aspect of growing, harvesting, and storage [548]. Specific guidelines for regulators regarding cannabis cultivation practices in the U.S. have been published by the AHPA. These standards include requirements for standard operating procedure documentation, employee safety training, security, and batch tracking [544]. Similarly, the American Herbal Pharmacopoeia has also released standards of quality control for cannabis cultivation.

In the Netherlands, Czech Republic, and Italy, medicinal cannabis must be produced under GMP-like conditions. *All* products must to be fully tested (by an independent laboratory) for cannabinoid content, absence of heavy metals, aflatoxins, pesticides (residue), and microbes to a level of <10 cfu. Standardization of cannabis and cannabis derivatives – according to the monograph of herbal medicines of the European Medicine Agency (EMA) – is mandatory and must be proven for each batch produced.

In Austria (AGES) and the UK (GW Pharmaceuticals, Ltd), cannabis is required to be produced under GAP, but any derivatives of this cannabis must be produced under GMP. Finished products must be standardized according to regular pharmaceutical products.

Good Manufacturing Practice for Cannabis

Many guidance documents are available for reference and use in the manufacturing of plant medicines and products, and any facility manufacturing products for human consumption should follow GMP. The World Health Organization has published guidelines on manufacturing botanical and herbal medicines, and the U.S. FDA has published guidance documents as well [549-552]. The AHPA manufacturing guidelines have a specific procedure for the *recall* of medical cannabis products, in the case of cannabis materials that do not meet “appropriate standards of identity, purity, strength, and composition and their freedom from contamination or adulteration.” The AHP cannabis monograph also sets limits for residues such as solvents and pesticides, heavy metals, bacteria, and fungi [214].

Good Laboratory Practices

Methods used to determine potency should be scientifically validated by laboratories for several criteria including, but not limited to: specificity, linearity, accuracy, precision, and ruggedness. The FDA and other organizations (i.e., AHPA, USP, and AHP) have provided extensive guidance documents that represent the current thinking on method validation and other aspects of good laboratory practices. There are further

international standards for analyzing medical cannabis products, which have been issued, for example, by the UN's Office of Drugs and Crime in their document, entitled *Recommended Methods for the Identification and Analysis of cannabis and cannabis products* [553].

Below are a few examples of applicable guidance from a regulatory perspective, for analytical method validation for new methods, or methods not outlined in existing international and national regulatory documents:

- USP–NF, Validation of Compendial Methods; USP pharmacopeia 35, United States Pharmacopeia Convention, Inc., Rockville, MD. May 1, 2012 – December 1, 2012.
- U.S. FDA, Center for Drug Evaluation and Research (CDER), Reviewer Guidance on Validation of Chromatographic Methods, November 1994.
- American Herbal Pharmacopoeia Cannabis Inflorescence. Standards of Identity, Analysis, and Quality Control (2013).

Quality control and quality standards for medicinal cannabis have been developed and adopted by 16 U.S. states and many countries, including Canada, Israel, the Netherlands, and the Czech Republic. Current standards are presently being appropriately applied or implemented through third party licensed certification bodies, for regulating cannabis and cannabis-related products for human consumption.

Both the AHP and AHPA documents point to Patient Focused Certification (PFC) for implementation of these standards. PFC has offices in Washington, DC and the Czech Republic. PFC is the only international program that can verify that a country, state, or region's cannabis standards are being followed.² PFC conducts both physical (i.e. site or facility) and documentation audits of the operation, to generate an audit report that is submitted to a review board. PFC's review board features experts that have served in regulatory and scientific roles in U.S. presidential administrations, at the USDA, in quality control laboratories, and related disciplines. PFC audited its first cannabis operations in the U.S. in 2013 and in Europe in 2015, and is now an option for regulators in every country, state, or region with medical cannabis access programs.

An undeniably successful public health outcome of product safety regulations has been demonstrated through numerous successful product recalls in Canada and the U.S. Recalls required the cooperation of government, manufacturers, and 3rd party certifying bodies, resulting in consumer protection [554-560].

To address public health concerns regarding the increasing availability of medical cannabis products, the scheduling status of cannabis needs to be thoughtfully and deliberately rescheduled (or descheduled), in order for producers, cultivators, manufacturers, laboratories, clinicians, researchers, and regulators to fully implement quality control standards for medical cannabis products.

Element (2) There are adequate safety studies.

Definition: "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

² For more information about the PFC program, see: www.patientfocusedcertification.org.

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." 57 Fed. Reg. 10499, 10506 (March 26, 1992).

DEA/FDA Evidence for Element 2

"The HHS stated that there are no adequate safety studies on marijuana. As indicated in their evaluation of Element #1, the considerable variation in the chemistry of marijuana complicates the safety evaluation. The HHS concluded that marijuana does not satisfy Element #2 for having adequate safety studies such that medical and scientific experts may conclude that it is safe for treating a specific ailment."

Available Scientific Data for Element 2

Cannabis products have been on the market for *decades*, and have shown clearly acceptable safety standards for use under medical supervision. Smoked, vaporized, or ingested cannabinoid medicine can deliver consistent amounts of active constituents, while toxic and/or lethal overdose of cannabis is not achievable and remains undocumented in either scientific or medical literature.

Sixteen states have adopted the national standards and guidance provided by the AHPA Cannabis Best Practices documents and the American Herbal Pharmacopoeia Cannabis Inflorescence Standards of Identity, Analysis, and Quality Control monograph. Federal standards are not available for cannabis and will not be produced by the USP while the plant is Schedule I, because the USP would thusly fall out of compliance with Drug Enforcement Administration (DEA) standards. Meanwhile, the FDA has approved several cannabis studies and a new IND program with a cannabis extract (marketed as Epidiolex), currently being administered to children in hospitals across the U.S with positive results.

While street marijuana arguably has a higher potential for abuse, standardized cannabis products accessed through a regulated program do not appear to have such high societal potential of abuse. Standardized cannabis-based medicines have been on the market for *decades* in the U.S. (Marinol and Nabilone), and whole-plant cannabis medicines are now available in 27 other countries (Bedrocan and nabiximols) [60]. Common sense dictates that self-administration of unstandardized, untested street drugs possesses a high potential for abuse, but the data addressing cannabis does not report, document, nor support the notion of significant abuse or divergence with standardized cannabis products. Cannabis should therefore be rescheduled because standardized preparations show very low potential for abuse and, therefore, possess minimal street value or resale value.

Based on current understanding of basic toxicity research – sedation, cytotoxicity, genotoxicity, etc. – cannabis and its components have a *uniquely* wide safety margin [36-39]. To date, there *has never been* a single well-documented case of human fatality attributable to an overdose of cannabis or its components, and no experimental or non-extrapolated LD₅₀ can be attributed to a toxic or lethal overdose of cannabis or a preparation thereof. No scientifically significant negative neuropsychological sequelae have yet been attributable to cannabis usage. The meta-analytical study of long-term cannabis use on neurocognitive functioning, results failed to find any substantial, systematic effect on users who were not concurrently intoxicated. Claims of brain damage and cerebral atrophy are not supported by current evidence. When controlling for pertinent variables such as age, gender, and history of alcohol use, research has not been able to show any association between the use of cannabis and changes in brain structures [59].

Short-term use of existing standardized medical cannabis and cannabis products appear to increase the risk of non-serious adverse events. Risks associated with long-term cannabis use are poorly characterized in published clinical trials and observational studies; however, the cognitive effects observed in long-term users do not appear to be permanent in nature [40]. With the exception of very limited studies on synthetic endocannabinoid system modulators, cannabis medicines do not appear to cause significant serious adverse events.

Arguably, some prior studies remain limited by a number of factors that need to be controlled in future investigations. Primarily, cannabis use and dosing needs to be confirmed in users with biological and chemical tests, as issues of dosing and patterns of use are confounding factors when not adjusted for.

Element (3) There are 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.” 57 Fed. Reg. 10499, 10506 (March 26, 1992).

DEA/FDA Evidence for Element 3

“As indicated in the HHS’s review of marijuana (HHS, 2015), there are no adequate or well-controlled studies that prove marijuana’s efficacy. The FDA independently reviewed (FDA, 2015) publicly available clinical studies on marijuana published prior to February 2013 to determine if there were appropriate studies to determine marijuana’s efficacy (please refer to FDA, 2015 and HHS, 2015 for more details). After review, the FDA determined that out of the identified articles, including those identified through a search of bibliographic references and 566 abstracts located on PubMed, 11 studies met the a priori selection criteria, including placebo control and double-blinding. FDA and HHS critically reviewed each of the 11 studies to determine if the studies met accepted scientific standards. FDA and HHS concluded that these studies do not “currently prove efficacy of marijuana” for any therapeutic indication due to limitations in the study designs. The HHS indicated that these studies could be used as proof of concept studies, providing preliminary evidence on a proposed hypothesis involving a drug’s effect.”

Available Scientific Data for Element 3

To date, more than 30,000 modern peer-reviewed scientific articles on the chemistry and pharmacology of cannabis and the cannabinoids have been published. More than 1,500 articles investigating the body's naturally-occurring endocannabinoids are published every year. In recent years, modern gold-standard placebo-controlled human trials have also been conducted.

At the time of writing this document, according to clinicaltrials.gov, there are *hundreds* of approved human research studies utilizing cannabinoids – A total of 144 are approved for THC, 96 are approved for CBD, and 559 are approved for cannabis. These studies are currently either completed, recruiting, approved, or in process. Due to the Schedule I status, however, medical cannabis preparations such as nabiximols and CBD-rich extracts are imported and cannot be manufactured in the U.S., even though they are licensed pharmaceutical products.

A 2009 review of clinical studies conducted over a 38-year period found that “nearly all of the 33 published controlled clinical trials conducted in the U.S. have shown significant and measurable benefits in subjects receiving the treatment,” [148]. The review's authors made particular effort to note that cannabinoids have the capacity for analgesia through neuromodulation in ascending and descending pain pathways, neuroprotection, and by anti-inflammatory mechanisms – all of which indicate that the cannabinoids found in cannabis have applications in significantly managing chronic pain, muscle spasticity, cachexia, and other variously debilitating conditions.

There is a wealth of clinical information available on the uses of standardized medical cannabis products. The FDA has approved new drug applications for cannabis products. For example, a CBD-rich extract (marketed as Epidiolex) is an imported, purified cannabis extract that has been approved for clinical use in children and is currently in clinical practice across several institutions in the U.S. Additionally, an inhaled cannabis study has recently been approved for investigating therapeutic effects in PTSD.

Cannabis currently has accepted medical uses in 42 states and the District of Columbia and, appropriately, its products have mandatory testing requirements. A cannabis nabiximols (Sativex), a whole-plant ethanolic extract, has generated more than 9,000 patient/years of modern clinical data for the treatment of chronic pain [126].

Currently, cannabis is most often recommended as a complementary or adjunctive medicine. However, there exists a substantial consensus amongst experts in the relevant disciplines – including the American College of Physicians – that cannabis and cannabinoid-based medicines have undeniable therapeutic properties that could potentially treat a wide spectrum of serious and chronic illnesses.

Element (4) The drug is accepted by qualified experts.

Definition: “[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.” 57 Fed. Reg. 10499, 10506 (March 26, 1992).

DEA/FDA Evidence for Element 4

“The HHS concluded that there is currently no evidence of a consensus among qualified experts that marijuana is safe and effective in treating a specific and recognized disorder. The HHS indicated that medical practitioners who are not experts in evaluating drugs cannot be considered qualified experts (HHS, 2015; 57 FR 10499, 10505). Further, the HHS noted that the 2009 American Medical Association (AMA) report entitled, “Use of Cannabis for Medicinal Purposes” does not conclude that there is a currently accepted medical use for marijuana. HHS also pointed out that state-level “medical marijuana” laws do not provide evidence of such a consensus among qualified experts.”

Available Scientific Data for Element 4

In ASA's 8-Factor analysis, under the section entitled “List of Medical and Scientific Organizations that have Issued Letter of Support for Medical Cannabis,” there are over 200 medical, scientific, health professionals, religious and community organizations who accept cannabis as a medicine and have issued letters in support of this medicine

In April 2016, the Federation of State Medical Boards (FSMB) adopted "Model Guidelines for the Recommendation of Marijuana in Patient Care."³

The National Cancer Institute – one of 11 federal agencies under the National Institutes of Health – changed its website to include cannabis as a Complementary Alternative Medicine, with possible benefits for people living with cancer.⁴

Statements from Qualified Experts and Medical Organizations

"Based on much evidence, from patients and doctors alike, on the superior effectiveness and safety of whole Cannabis (marijuana) compared to other medicines for many patients — suffering from the nausea associated with chemotherapy, the wasting syndrome of AIDS, and the symptoms of other illnesses ... we hereby petition the Executive Branch and the Congress to facilitate and expedite the research necessary to determine whether this substance should be licensed for medical use by seriously ill persons." - **American Academy of Family Physicians**

The American Medical Association *"urges that marijuana's status as a federal Schedule I substance be reviewed with the goal of facilitating the conduct of clinical research and development of cannabinoid-based medicines."*

The American College of Physicians *"urges an evidence-based review of marijuana's status as a Schedule I controlled substance to determine whether it should be reclassified to a different schedule."*

The American Public Health Association *"adopted a resolution [...] which urged federal and state drugs laws to exclude Marijuana as a narcotic drug," and "conclude[d] that Cannabis was wrongfully placed in Schedule I of Controlled Substances, depriving patients of its therapeutic potential."*

"Marijuana should be available for appropriate medicinal purposes, when such use is in accordance with state law, and that physicians who recommend and prescribe marijuana for medicinal purposes in states where such use is legal, should not be censured, harassed, prosecuted or otherwise penalized by the federal government." - **American Preventive Medical Association**

"The Texas Medical Association supports (1) the physician's right to discuss with his/her patients any and all possible treatment options related to the patients' health and clinical care, including the use of marijuana, without the threat to the physician or patient of regulatory, disciplinary, or criminal sanctions; and (2) further well-controlled studies of the use of marijuana with seriously ill patients who may benefit from such alternative treatment." - **Texas Medical Association**

The Rhode Island Medical Society has stated that "[T]here is sufficient evidence for us to support any physician-patient relationship that believes the use of marijuana will be beneficial to the patient."

"The definitive review of scientific studies ... found medical benefits related to pain relief, control of nausea and vomiting, and appetite stimulation ... While there are a variety of ways of supplying marijuana for

³ See www.medicalCannabis.com/about/health-care-professionals/supporting-organizations.

⁴ See <http://www.cancer.gov/about-cancer/treatment/cam/hp/Cannabis-pdq> - section/all.

medical use, serious consideration should be given to the 1997 recommendation ... that the FDA reclassify marijuana from Schedule I and provide a consistent, safe supply.” - New York County Medical Society

“The American Medical Student Association strongly urges the United States Government ... to meet the treatment needs of currently ill Americans by restoring the Compassionate (Investigational New Drug) program for medical marijuana, and ... reschedule marijuana to Schedule II of the Controlled Substances Act, and ... end the medical prohibition against marijuana.” - American Medical Student Association

“The National Nurses Society on Addictions urges the federal government to remove marijuana from the Schedule I category immediately, and make it available for physicians to prescribe. NNSA urges the American Nurses’ Association and other health care professional organizations to support patient access to this medicine.” - National Nurses Society on Addictions

“The American Cancer Society supports the need for more scientific research on cannabinoids for cancer patients, and recognizes the need for better and more effective therapies that can overcome the often debilitating side effects of cancer and its treatment. The Society also believes that the classification of marijuana as a Schedule I controlled substance by the US Drug Enforcement Administration imposes numerous conditions on researchers and deters scientific study of cannabinoids. Federal officials should examine options consistent with federal law for enabling more scientific study on marijuana.” - American Cancer Society

“The Society supports the rights of people with MS to work with their MS health care providers to access marijuana for medical purposes in accordance with legal regulations in those states where such use has been approved. In addition, the Society supports advancing research to better understand the benefits and potential risks of marijuana and its derivatives as a treatment for MS.” - National Multiple Sclerosis Society

“The Epilepsy Foundation supports the rights of patients and families living with seizures and epilepsy to access physician directed care, including medical marijuana. Nothing should stand in the way of patients gaining access to potentially life-saving treatment. If a patient and their healthcare professionals feel that the potential benefits of medical marijuana for uncontrolled epilepsy outweigh the risks, then families need to have that legal option now — not in five years or ten years. For people living with severe uncontrolled epilepsy, time is not on their side. This is a very important, difficult, and personal decision that should be made by a patient and family working with their healthcare team.” - Epilepsy Foundation

“(T)he Leukemia & Lymphoma Society supports legislation to remove criminal and civil sanctions for the doctor-advised, medical use of marijuana by patients with serious physical medical conditions.” - Leukemia & Lymphoma Society

Medical schools are teaching required coursework which includes the endocannabinoid system and the therapeutic applications of cannabis. One example, theanswerpage.org, a Harvard University based CME, is educating physicians about the benefits of the medical uses of cannabis. This has led to the creation of

clinical cannabis certification for physicians; an educational program that is required for physicians to recommend medical cannabis in states such programs.⁵

Element (5) The scientific evidence is 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." 57 Fed. Reg. 10499, 10506 (March 26, 1992).

DEA/FDA Evidence for Element 5

"The HHS concluded that the currently available data and information on marijuana is not sufficient to allow scientific scrutiny of the chemistry, pharmacology, toxicology, and effectiveness. In particular, scientific evidence demonstrating the chemistry of a specific Cannabis strain that could provide standardized and reproducible doses is not available."

Available Scientific Data for Element 5

One of the criteria preventing the rescheduling of cannabis is the notion that information about this medicine is not widely available. There are tens of thousands of peer reviewed articles available through online portals, journal websites, and other resources for health professionals to access clinical information about cannabis, including but not limited to: Springer, Wiley, Pubmed, Public Libraries, medical and graduate school libraries, and websites of expert groups such as Americans for Safe Access, theAnswerpage.org, and the International Cannabis and Cannabinoid Institute.

The Internet has also revolutionized cannabinoid research and science, by allowing the generation of, and access to, large amounts of information that would have previously been nearly impossible to obtain. People across the globe can now access innumerable sources (a search for 'cannabis research' through web of science alone yields 120,000 separate articles) of previously unavailable scientific and clinical information.

Furthermore, the nabiximol Sativex is extracted from two fully-characterized, standardized cannabis chemovars, one of which is called Skunk No.1. It is odd, therefore, that the FDA would claim, "scientific evidence demonstrating the chemistry of a specific cannabis strain that could provide standardized and reproducible doses is not available." While according to NIDA, DEA, FDA, and RTI, University of Mississippi researchers have grown *several* types of cannabis strains for decades, which are allegedly turned into standardized products for clinical research under the supervision and participation of NIDA, DEA, FDA and RTI⁶.

⁵ For more information about Cannabis Care Certification, see <http://cannabiscarecertification.org>.

⁶ See Thomas, B. F., & ElSohly, M. (2015). *The Analytical Chemistry of Cannabis. Quality Assessment, Assurance, and Regulation of Medicinal Marijuana and Cannabinoid Preparations*. Elsevier.

It is simply disingenuous for an organization to state that no standardized cannabis product exists, while simultaneously licensing both the production and distribution of such products.

VII. Evaluating the DEA's Statement 3) Marijuana lacks accepted safety for use under medical supervision.

DEA's Evidence Regarding Safety

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

Available Scientific Data Regarding Safety

According to the CSA statute, as cited by the DEA in their evaluation:

"The CSA defines marijuana as the following:

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

This definition means that THC and CBD isolated from the plant are "resins". Yet, the DEA states clearly under item 3:

"At present, there are no marijuana products approved by the U.S. Food and Drug Administration (FDA), nor is marijuana under a New Drug Application (NDA) evaluation at the FDA for any indication."

This statement is incorrect. Marinol, an FDA approved form of pure THC, can now be generically made from THC isolated from cannabis plants, such as those from the University of Mississippi. Marinol started out as synthetic THC, but can now be plant-derived, however the DEA report is implying that cannot occur. No companies have admitted to pursuing this path, but it is an approved generic form of Marinol by the FDA. As defined by the CSA, both Epidiolex® and Sativex® are resinous cannabis extracts, and are presently undergoing clinical studies in the United States. According to GW Pharmaceutical's website, Phase III trials got underway in 2015, utilizing the cannabis extract Sativex® with FDA approval. Both standardized cannabis extracts marketed by GW Pharmaceutical (Epidiolex® and Sativex®) continue to be imported and are undergoing clinical study in the United States.

This arbitrary interpretation of the CSA is used to simultaneously and systematically prevent any discussion of the nearly 100 clinical trials completed with cannabis products while, at the same time,

THC, CBD, Sativex, and NIDA-generated cannabis cigarettes are considered “marijuana” if the user is prosecuted.

This is another example of how the DEA report seems to follow a more politically-driven agenda, rather than one of modern science and medicine. By attempting to redefine the CSA as meaning *only* whole plant cannabis, when it was intended to include derivatives and extracts thereof, the DEA is allowed to generate reports and statements that are not based on scientific research. The systematic use of biased methods to generate reports on scientific data leaves large swaths of modern cannabinoid research unheeded. Hence, the clinical references in the HHS 8-factor analysis consists of less than 1% of the discussed research. If the DEA report had included more than two clinical studies in their HHS 8-factor analysis, this would be a different conversation.

VIII. Conclusion

The goal of this comparative analysis is to objectively examine the data used in the DEA's determination of their denial to allow a petition to reschedule cannabis, and to compare it to the prevailing scientific data on the medical value of cannabis. While we agree with portions of the DEA report – such as the lack of evidence to support either diversion or black market sales or the “gateway” hypothesis, we do not agree with either the process or the evidence upon which their denial was based. By applying politics and ideology, while excluding current scientific information, the DEA can only further the passage of truly inaccurate statements, which might then be used to establish inaccurate laws regarding health and medicine.

Ideology and politics should never be allowed to eclipse the available scientific and clinical truth in matters of medicine or the health of our citizenry. This DEA report highlights how the use of engrained, historically inaccurate political beliefs to arbitrarily interpret the CSA has been exploited at the expense of public health. This stems from the fact that the DEA alone, inexplicably, has been allowed to determine how “medicine” is defined in this country, with little to no accountability.

Unfortunately, cannabis will never be rescheduled under these Catch-22-like circumstances. The CSA is arbitrarily used, on one hand, to exclude all medical research on derivatives of cannabis from their report...while, on the other hand, it is used to prosecute anyone in possession of those derivatives. Persistent misinterpretation of existing laws, coupled to lack of scientific knowledge, results in a very dangerous and socially destructive policy for a government enforcement agency.

The documents submitted in the report for the denial of the petitions are contradictory, and would appear to have little or no relevance to either contemporary cannabinoid science or medicine. Even so, as there were no clear negative public health implications relating to moving cannabis out of Schedule I status presented therein, it would appear that the DEA has chosen a disingenuous, overtly biased response to legitimate medicinal cannabinoid progress.

This type of response is responsible for the pitfalls of the current cannabis market by preventing the implementation of suitable controls. Such as addressing the pesticide contamination in the legal adult use

markets as a key case in point. Interference with product safety that results directly from ideological policies, is a dereliction of responsibility that supports a major public health threat.

Recommendations

Pass CARERS

Congress should pass [The Compassionate Access, Research Expansion, and Respect for States \(CARERS\) Act \(S. 683, H.R. 1538\)](#) as introduced in 2015 which, in addition to rescheduling cannabis and removing cannabidiol (CBD) from the schedule entirely, allows states to establish medical cannabis access laws and product safety regulations without interference by the federal government, and removes current obstacles to research. The CARERS Act is currently stalled in the Senate Judiciary Committee, with Chairman Chuck Grassley (IA) refusing to hold a vote.

Update Information on DEA Website and Educational Materials

We also recommend that the DEA update the following on their website and in education materials provided online. The updates should be made to reflect the information from the current DEA report.

1. DEA statements regarding adverse health effects related to cannabis

- “[According to an Australian study,] there is now conclusive evidence that smoking cannabis hastens the appearance of psychotic illnesses by up to three years.”⁷
- “Marijuana’s effects on these abilities may last a long time or *even be permanent*.”⁸

Requested change to reflect current information from the DEA’s report:

On page 12, the DEA report states, “*Abundant scientific data are available on the neurochemistry, toxicology, and pharmacology of marijuana.*”⁹

On page 20, the DEA report states, “*cannabis-associated cognitive deficits are reversible and related to recent cannabis exposure, rather than irreversible and related to lifetime use.*”¹⁰

⁷ From a document entitled *Dangerous and Consequences of Marijuana Abuse* (page 12):
<https://www.dea.gov/docs/dangers-consequences-marijuana-abuse.pdf>

⁸ And from From “DrugFacts: Marijuana.” Link available through DEA website/a DEA resource site:
<https://www.drugabuse.gov/publications/drugfacts/marijuana>

⁹ Link to paragraph: <https://www.federalregister.gov/articles/2016/08/12/2016-17954/denial-of-petition-to-initiate-proceedings-to-reschedule-marijuana#p-81>

¹⁰ Link to paragraph: <https://www.federalregister.gov/articles/2016/08/12/2016-17954/denial-of-petition-to-initiate-proceedings-to-reschedule-marijuana#p-123>

On page 22, the DEA report states, *"At present, the available data do not suggest a causative link between marijuana use and the development of psychosis."*¹¹

2. Statements from DEA regarding the "gateway theory"¹²

- *"Teens who experiment with marijuana may be making themselves more vulnerable to heroin addiction later in life, if the findings from experiments with rats are any indication. Cannabis has very long-term, enduring effects on the brain..."* (pg. 37)
- *"Marijuana use in early adolescence is particularly ominous. Adults who were early marijuana users were found to be five times more likely to become dependent on any drug, eight times more likely to use cocaine in the future, and fifteen times more likely to use heroin later in life."* (pg. 38)
- *"Marijuana is a frequent precursor to the use of more dangerous drugs and signals a significantly enhanced likelihood of drug problems in adult life."* (pg. 37)

Below are the requested changes to reflect the current information from the DEA report:

On page 43, the DEA report states, *"Overall, research does not support a direct causal relationship between regular marijuana use and other illicit drug use."*¹³

On page 44, the DEA report states, *"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."*¹⁴

On page 162, the DEA report states, *"The HHS reviewed the clinical studies evaluating the gateway hypothesis in marijuana and found them to be limited."* The DEA goes on to say, *"The HHS cited several studies where marijuana use did not lead to other illicit drug use."*¹⁵

On page 162, the DEA report states, *"Based on these studies among others, the HHS concluded that although many individuals with a drug abuse disorder may have used marijuana as one of their first illicit*

¹¹ Link to paragraph:

<https://www.federalregister.gov/articles/2016/08/12/2016-17954/denial-of-petition-to-initiate-proceedings-to-reschedule-marijuana#p-131>

¹²https://www.dea.gov/docs/marijuana_position_2011.pdf

¹³ Link to paragraph: <https://www.federalregister.gov/articles/2016/08/12/2016-17954/denial-of-petition-to-initiate-proceedings-to-reschedule-marijuana#p-237>

¹⁴ Link to paragraph: <https://www.federalregister.gov/articles/2016/08/12/2016-17954/denial-of-petition-to-initiate-proceedings-to-reschedule-marijuana#p-242>

¹⁵ Link to paragraph: <https://www.federalregister.gov/articles/2016/08/12/2016-17954/denial-of-petition-to-initiate-proceedings-to-reschedule-marijuana#p-956>

drugs, this does not mean that individuals initiated with marijuana inherently will go on to become regular users of other illicit drugs.”¹⁶

Over 40 years ago the “gateway” hypothesis of cannabis was proposed. The report concludes predictably, that the gateway theory of cannabis is not supported by the evidence. We agree that the hypothesis attempted but failed to predict that cannabis use leads to the addiction of other drugs.

3. Statements from the DEA regarding cannabis and cancer¹⁷

“Marijuana smoking has been implicated as a causative factor in tumors of the head and neck and of the lung.”(pg.34)

“Marijuana takes the risks of tobacco and raises them. Marijuana smoke contains more than 400 chemicals and increases the risk of serious health consequences, including lung damage.”(pg 36)

Below are the requested changes to reflect the current information from the DEA report:

“However, in a large clinical study with 1,650 subjects, no positive correlation was found between marijuana use and lung cancer (Tashkin et al., 2006). This finding held true regardless of the extent of marijuana use when both tobacco use and other potential confounding factors were controlled. The HHS concluded that new evidence suggests that the effects of smoking marijuana on respiratory function and cancer are different from the effects of smoking tobacco (Lee and Hancox, 2011).”¹⁸

“The DEA further notes the publication of recent review articles critically evaluating the association between marijuana and lung cancer. Most of the reviews agree that the association is weak or inconsistent (Huang et al., 2015; Zhang et al., 2015; Gates et al., 2014; Hall and Degenhardt, 2014). Huang et al. (2015) identified and reviewed six studies evaluating the association between marijuana use and lung cancer and the authors concluded that an association is not supported most likely due to the small amounts of marijuana smoked in comparison to tobacco. Zhang et al. (2015) examined six case control studies from the US, UK, New Zealand, and Canada within the International Lung Cancer Consortium and found that there was a weak association between smoking marijuana and lung cancer in individuals who never smoked tobacco, but precision of the association was low at high marijuana exposure levels...overall association is weak between marijuana use and lung cancer especially when controlling for tobacco use.”¹⁹

¹⁶ Link to paragraph: <https://www.federalregister.gov/articles/2016/08/12/2016-17954/denial-of-petition-to-initiate-proceedings-to-reschedule-marijuana#p-959>

¹⁷ From DEA Position on Marijuana document:
https://www.dea.gov/docs/marijuana_position_2011.pdf

¹⁸ Link to paragraph: <https://www.federalregister.gov/articles/2016/08/12/2016-17954/denial-of-petition-to-initiate-proceedings-to-reschedule-marijuana#p-860>

¹⁹ Link to paragraph: <https://www.federalregister.gov/articles/2016/08/12/2016-17954/denial-of-petition-to-initiate-proceedings-to-reschedule-marijuana#p-861>