

November 23, 2007

Via Regular Mail

Deputy Administrator
Drug Enforcement Administration
Washington, DC 20537
ATTENTION: DEA Federal Register Representative/ODL

RE: Docket No. DEA-308P; Proposed Rule; Technical Amendment to Listing in Schedule III of Approved Drug Products Containing Tetrahydrocannabinols; 72 Fed. Reg. 54226, September 24, 2007

Public Comment of Americans for Safe Access

Dear Madam/Sir:

Herein is the public comment of Americans for Safe Access ("ASA") regarding the above-referenced proposed rule.

A. Interest of ASA

ASA is a non-profit advocacy organization dedicated to advancing safe and legal access to cannabis therapeutics and research. Dronabinol, or Delta-9-THC, is the name of a particular isomer of a class of chemicals known as Tetrahydrocannabinols ("THC"), and is one of the more than 60 cannabinoids present in whole-plant cannabis. As such, ASA has a direct interest in the scheduling of drug products containing THC. ASA's interest includes, without limitation, an interest in assuring that drug products containing THC are assigned to the respective schedules under the Controlled Substances Act and the Code of Federal Regulations with due regard to the proven medical benefits of THC and other cannabinoids.

B. ASA's position on the Proposed Changes to 21 C.F.R. § 1308.13(g)

ASA respectfully submits regarding the proposed changes to the wording of the current Schedule III designation of the dronabinol drug products at 21 C.F.R. § 1308.13(g) that:

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1. The Proposed Changes to 21 C.F.R. § 1308.13(g) Recognize the Medical Benefits of THC and the Value of Whole-Plant Cannabis in Extracting THC, and Will Likely Create Greater Access for Patients to Cheaper, Naturally-Derived Cannabis-Based Drugs

The DEA's September 24, 2007, proposal would add additional drugs to the Hallucinogenic Substances subsection of Schedule III 21 C.F.R. 1308.13(g). Currently, only dronabinol suspended in sesame oil, encapsulated in a softgel capsule (marketed as Marinol), is currently scheduled in Schedule III, and all other cannabis-related substances remain in Schedule I. The proposed rule would expand Schedule III to also include

"any drug product in tablet or capsule form containing natural dronabinol (derived from the cannabis plant) or synthetic dronabinol (produced from synthetic materials) for which an abbreviated new drug application (ANDA) has been approved by the FDA under § 505(j) of the Federal Food, Drug, and Cosmetic Act." Fed. Reg., Vol. 72, No. 184, 54229 (September 24, 2007).

According to the proposed rule, pending ANDA approval, softgel capsules with synthetic or naturally-derived dronabinol and a non-sesame oil liquid, hard-shell capsules with dry powdered synthetic or naturally-derived dronabinol, and tablet and oral liquid forms of synthetic or naturally-derived dronabinol would have the capacity to become Schedule III prescribable drugs. Fed. Reg., Vol. 72, No. 184, 54226, 54227 (September 24, 2007). ASA approves of this proposed change by the DEA because it acknowledges the obvious medical benefits of THC, recognizes the value of whole-plant cannabis used to extract the phytocannabinoid THC, and it will likely create greater access for patients in the short term to cheaper, naturally derived cannabis-based drugs.

Primarily, the proposed rule is a positive step because in it, the DEA acknowledges, only for the second time (Marinol was the first in 1986), the obvious medical benefits of THC/dronabinol. These proposed changes also represent progress because they implicitly recognize the value of whole-plant cannabis and its capacity to extract naturally occurring THC that is bioequivalent to synthetic THC. Products are bioequivalent if there is no significant difference in the rate and extent to which the active ingredient

or active moiety becomes available at the site of drug action. 21 C.F.R. § 320.1. In its comments to DEA (Rhodes Technologies “Comment and Request for Hearing”, re: Docket No. DEA-308P, October 24, 2007.), Rhodes Technologies notes negatively that THC extracted from whole-plant cannabis will contain certain impurities. October 24, 2007 Rhodes Technologies Letter to DEA, pg 7. ASA would not deny the presence of these impurities, but disagrees with Rhodes on their effect on naturally-derived cannabis-based drugs. ASA appreciates that the proposed rule recognizes that this naturally derived formulation (which may include some minor impurities) has the capacity to have the same active ingredient, strength, dosage form, and route of administration as Marinol and to be bioequivalent to Marinol. To some degree, the impurities concern fails to acknowledge that at present Marinol possesses some level of impurities, and depending upon the process a particular manufacturer uses to extract dronabinol, more or less impurities may be present. However, ASA believes that any impurities present would be negligible, and of course any pharmaceutical product developed under the proposed rule would still be subject to FDA safety and other evaluations.

This proposed change is also a positive development because its will likely result in greater access for patients to less expensive, naturally derived cannabis-based drugs in the short term. This result is likely for several reasons. Generic drugs, drugs that are produced and distributed without patent protection (and approved by the FDA under 21 U.S.C. 355 § 505(j)), are generally much cheaper than brand-name drugs, such as Marinol. This occurs because the drug companies incur fewer costs in creating the generic drug, and are therefore able to maintain profitability while offering the drug at a lower cost to consumers. Generic manufacturers do not incur the cost of drug discovery, and instead are able to reverse-engineer known drug compounds to allow them to manufacture bioequivalent versions. Generic manufacturers also do not bear the burden of proving the safety and efficacy of the drugs through clinical trials, since these trials have already been conducted by the brand-name company, and benefit from FDA’s Abbreviated New Drug Application process.

Additionally, as Rhodes Technologies notes negatively in its Letter to DEA, the broadness of the proposed additional definition of dronabinol formulations suggests that many different types of drugs and mediums may become available as a result of this change. October 24, 2007 Rhodes Technologies Letter to DEA, pg 4 & 6. ASA instead applauds the DEA’s choice of a broad definition, as it may incentivize research, increasing the likelihood that several non-Marinol cannabis-based drugs will be available on the market in the near future. Alternatively, if dronabinol remains in

Schedule I, it is unlikely that research will increase, as it is much more difficult and expensive to research Schedule I drugs.

Finally, the naturally derived cannabis-based drugs will specifically be less expensive than those made from synthetic THC. Currently, Marinol, which uses synthetic THC, is very expensive to produce, and the cost of development is passed on to patients and/or their insurance companies in the form of higher priced prescription drugs. A drug producer, extracting the cannabinoid THC from whole-plant cannabis (a much simpler process than the creation of the synthetic) will be able to produce naturally derived dronabinol at a substantially reduced cost.

2. The Proposed Changes to 21 C.F.R. § 1308.13(g) are Inconsistent, Recognizing Whole-Plant Cannabis but Refusing to Reschedule THC, and Other Non-Psychoactive Cannabinoids to Facilitate Research and Development of a Wide Variety of Cannabis-based Medicines

As previously mentioned in Section B.1., the proposed changes to 21 C.F.R. § 1308.13(g) recognize the validity of whole-plant cannabis and its ability to produce the phytocannabinoid, THC, which is bioequivalent to synthetic Dronabinol. However, this recognition is too conservative, and the DEA is missing an opportunity to be consistent.

The proposed changes should also reschedule many of the other naturally occurring phytocannabinoids without requiring an abbreviated new drug application, so as to incentivize the research and development of cannabis-based pharmaceutical products to satisfy the diverse medical needs of patients.

Numerous peer-reviewed studies characterize in detail the chemistry of cannabis. The active components of the cannabis plant are well-known and thoroughly described, as are the mechanisms of biologic action in humans. The primary psychoactive component, delta-9 tetrahydrocannabinol, was synthesized in the 1960s and is the subject of the proposed rule change. However, it must be noted that, since the 1960s, researchers have isolated, synthesized and stereochemically defined 66 cannabinoid components, as well as scores of inactive metabolites. Of those 66 cannabinoids, most are closely related, falling into only 10 groups, many of which differ by only a single chemical moiety, suggesting they are merely midpoints along biochemical pathways, such as degradation products,

precursors, or byproducts. (Ross, SA. *et al.*, Constituents of Cannabis Sativa L. XXVIII. A review of the natural constituents: 1980-1994. *J. Pharm Sci.*, 4:1-10 (1995); and, Turner CE. *Et al.*, Constituents of Cannabis sativa L. XVII. A review of the natural constituents. *J. Natural Products* 43:169-234 (1980). Moreover, the biologic pathways of action are also well described, as are the CBI and CB2 receptor sites of the endogenous cannabinoid system, with which marijuana and its active compounds interact. Mechoulam R. *et al.* From gan-zi-gun-nu to anandamide and 2-arachidonoylglycerol : the ongoing story of cannabis . *Natural Products Reports* 16 :131-143 (1999); Russo EB. Future of cannabis and cannabinoids in therapeutics . *Journal of Cannabis Therapeutics* (3/4):163-174 (2003); McPartland JM, Russo EB. Cannabis and cannabis extracts : Greater than the sum of their parts? *Journal of Cannabis Therapeutics* 2001(3/4) :103-132 (2001); and ElSohly M. 2002. Chemical constituents of Cannabis. In Grotenhermen F, Russo EB (Eds.), *Cannabis and cannabinoids: pharmacology, toxicology and therapeutic potential*. NY: Haworth Press (2002).

Thirty years ago, when THC and other cannabinoids were placed in Schedule I, nothing was known about the endocannabinoid system. However, recent discoveries have generated a great deal of interest in identifying opportunities for the development of cannabis-based medicines. This is an area that is ripe for research. Yet, despite the fact that THC is the only known psychoactive cannabinoid, and despite the DEA metric that demands that a non-Schedule I drug demonstrate a lower potential for abuse than a Schedule I drug, non-psychoactive cannabinoids such as cannabidiol ("CBD") and cannabinol ("CBN") with recognized therapeutic potential remain in Schedule I. The proposed rule limits research and development to formulations of dronabinol, not the many other cannabinoids that unto themselves or in combination with one another provide demonstrable medical benefit.

ASA instead insists that the DEA should not only make the proposed rule change regarding THC, and, because it would be consistent with the DEA's new stance on whole-plant cannabis and also good public policy, the DEA should initiate another proposed rule change that reschedules a wide array of natural, non-psychoactive phytocannabinoids to support the research and development of a wider variety of cannabis-based medicines. Research suggests that the beneficial therapeutic effects of cannabis may result from the interaction, or synergy, among various cannabinoids. This helps to explain why medicines developed from whole-plant extracts may be more effective than single cannabinoid drugs developed from synthetic compounds. For instance, Sativex is a cannabis-based medicine, which

combines both THC and CBD to produce an entirely different therapeutic potential than THC alone, has been developed by UK-based GW Pharmaceuticals, and has been approved for use in Canada and is undergoing clinical trials in Europe and the United States.

3. The Proposed Changes to 21 C.F.R. § 1308.13(g) are Deficient in That They do not Address the NIDA Monopoly on the Medical Cannabis Supply and its Resulting Restriction of Whole-Plant Cannabis Research

As previously mentioned in Section B.1., the proposed changes to 21 C.F.R. § 1308.13(g) recognize the validity of whole-plant cannabis and its ability to produce dronabinol bioequivalent to synthetic dronabinol. However, this recognition is too conservative, and the DEA is missing an opportunity to address the larger issue. The proposed changes should also recognize the problem that the NIDA monopoly on the supply of medical cannabis creates, and include proposed solutions to the resulting research impediments. Specifically, the DEA should accept the opinion of its own U.S. Department of Justice-appointed Administrative Law Judge (ALJ) Mary Ellen Bittner, who urges the DEA to grant a license to Professor Lyle Craker to cultivate research-grade cannabis for distribution exclusively to federally approved researchers, which would greatly facilitate research on the therapeutic value of cannabis and access to its naturally derived constituent cannabinoids, specifically THC. U.S. Dept. of Justice, Drug Enforcement Administration, "In the Matter Lyle E. Craker, Ph.D., Docket No. 05-16, Opinion and Recommended Ruling, Findings of Fact, Conclusions of Law, and Decision of Administrative Law Judge," Mary Ellen Bittner, Administrative Law Judge, February 12, 2007, p. 87 *available at* <http://www.maps.org/mmj/DEAlawsuit.html>.

a. Background

Despite the fact that federal law clearly requires adequate competition in the manufacture of Schedule I and II substances, the DEA has flouted that law since 1968 and has given the National Institute on Drug Abuse (NIDA) the only Schedule I bulk manufacturers' license for cannabis, creating an unjustified monopoly on cannabis cultivation for legitimate medical and research purposes in the U.S. Because of NIDA's obstruction, even researchers with FDA-approved protocols have extreme difficulty obtaining cannabis. DEA helps to protect NIDA's monopoly by refusing to grant competitive licenses for cannabis production to any other entities.

Currently, the only way for the FDA to find that cannabis, or its constituent compounds, meets the necessary standards in order to declare it a "medicine" under federal law is for privately-funded sponsors to develop a drug product on which to conduct FDA-approved clinical trials. Unfortunately, NIDA has the only license to legally cultivate research cannabis and this monopoly fundamentally obstructs privately-funded research. NIDA states that its mission is "to lead the Nation in bringing the power of science to bear on drug abuse and addiction." Available at <http://www.drugabuse.gov/About/AboutNIDA.html>. This mission does not include, and in fact may actively conflict with, studying the beneficial uses of cannabis or advocating for such research.

NIDA currently contracts with the University of Mississippi to cultivate its cannabis for legal research purposes and it discriminates against researchers studying the beneficial uses of cannabis. When researchers with FDA-approved protocols have requested cannabis for research regarding its medicinal use, they have faced arbitrary and lengthy delays and eventual rejection. For example, NIDA waited more than two years to finally reject the initial request of Chemic Labs, a DEA-licensed analytical lab, to purchase 10 grams of cannabis for privately sponsored research into the development of vaporizers, a non-smoking delivery system recommended by the 1999 Institute of Medicine report. NIDA has also refused to provide cannabis to two other privately sponsored, FDA-approved protocols that sought to evaluate cannabis for AIDS wasting syndrome (IND #43-542) and for migraines (IND #58-177). Additionally, even if NIDA chose to release cannabis from its University of Mississippi facility to an FDA-approved study, progress in research would likely still remain stagnant because the quality of NIDA's cannabis supply is extremely low-grade and consequently will yield questionable data.

b. DEA should grant Professor Lyle Craker's Petition for a Schedule I Bulk Manufacturer's License to End the Federal Monopoly on Legal Research Cannabis, and to Ensure Competition of Cultivation of Higher-Grade Cannabis for Research purposes

For six years, Professor Lyle Craker, Director, Medicinal Plant Program, University of Massachusetts-Amherst, has been struggling to petition DEA for a bulk manufacturers' license so that he may create a privately-funded facility at the University to grow cannabis exclusively for FDA-approved

studies designed to evaluate the potential medical value of cannabis. If DEA were to grant Prof. Craker's petition, it would end the NIDA monopoly on legal research cannabis, and ensure a larger supply of higher-grade cannabis.

In February, DEA's own Administrative Law Judge (ALJ) Mary Ellen Bittner issued an 87-page opinion, findings of fact, and recommended ruling urging an end to the federal monopoly on the supply of cannabis that can be used in FDA-approved research. U.S. Dept. of Justice, Drug Enforcement Administration, "In the Matter Lyle E. Craker, Ph.D., Docket No. 05-16, Opinion and Recommended Ruling, Findings of Fact, Conclusions of Law, and Decision of Administrative Law Judge," Mary Ellen Bittner, Administrative Law Judge, February 12, 2007, p. 87 *available at* <http://www.maps.org/mmj/DEAlawsuit.html>. Judge Bittner determined that "respondent's registration to cultivate cannabis would be in the public interest," and recommended that DEA grant the license to Professor Craker.

DEA Administrator should accept Judge Bittner's recommendation that DEA grant a Schedule I bulk manufacturer license to Prof. Lyle Craker in order to establish an independent, privately-funded facility to produce cannabis exclusively for federally approved and privately funded research.

C. Conclusion

The September 24, 2007, proposal should be adopted as proposed, and the DEA should begin further consideration of rescheduling other cannabinoids and accept ALJ Bittner's recommendation to grant a Schedule I bulk manufacturer license to Prof. Lyle Craker in order to remove research barriers.

Respectfully yours,

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