STATE OF SOUTH DAKOTA

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MARTY J. JACKLEY
ATTORNEY GENERAL

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CHIEF DEPUTY ATTORNEY GENERAL

August 19, 2016

Robert M. Califf
Commissioner of Food and Drugs Administration
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Springs, MD 20993

Chuck Rosenberg
Acting Administrator of the Drug Enforcement Administration
Drug Enforcement Administration
9701 Morrissette Drive
Springfield, VA 22152

Dear Dr. Califf and Mr. Rosenberg,

As South Dakota's Attorney General and former United States Attorney, I am focused on making South Dakotans healthier and safer. I am writing this letter to add my voice to the discussion about marijuana and its legality as it is a growing concern for law enforcement and those with real medical needs around the country. Based on DEA's recent determination that marijuana will remain listed as a Schedule I drug under the Controlled Substances Act, it has been determined to maintain no accepted medicinal value as a matter of federal law. This is applicable to all forms of marijuana, including CBD oils. As I am sure you can understand, the use of marijuana, cannabinoids, and other forms or derivatives has become an increasingly important discussion in our states.

As Attorney General, I am hopeful for the sake of children and adults suffering medical conditions that research will conclude derivatives of marijuana will help treat a child experiencing seizures or the pain of a cancer patient. If medical research reaches this milestone, I strongly believe that three important conditions must be satisfied for public health and safety reasons:

1. There needs to be FDA approval for marijuana or one or more of its derivatives as a safe and effective drug;
2. A South Dakota doctor to prescribe the drug; and
3. A South Dakota pharmacist to dispense the drug.

I understand that conditions two and three are outside your purview but condition one, as the initial step, is not. There is a push in the states to legalize marijuana, either completely including for recreational use, or in part as a medical treatment. Having multiple jurisdictions with inconsistent regulations and rules has created challenges for the states.

It is because of this, I am urging the FDA to consider an accelerated approval process for marijuana derivatives for medical purposes only. Either way, there needs to be an answer as to the efficacy of cannabinoid CBD, for the treatment of those stricken with epilepsy or other conditions that might be lessened with CBD treatments based on sound scientific research. I am heartened to learn that Sativex, a pharmaceutical cannabis spray and Epidiolex, a pharmaceutical purified CBD by GW Pharmaceuticals has been approved by the FDA for "fast track" designation to help expedite it through the clinical trial process.

It is my understanding that Sativex is targeted specifically at reducing pain among cancer patients and spasticity among MS patients while Epidiolex has shown positive Phase 3 Trial Results in the treatment of Lennox-Gastaut and Dravet syndrome. This is truly a benevolent and compassionate endeavor, and I hope we experience strides in research for curing or better treating severe, intractable childhood epilepsy.

While I do not endorse any particular area of research over another, I believe that the public health aspects justify that the FDA and DEA revisit the research restrictions as it relates to Schedule I drugs, with an eye towards medical research in controlled environments. For these reasons, I urge you to assist in the determination of whether these developing cannabinoid medicines present medical opportunities or are no more effective than current treatment options. Should you have any questions or concerns, please do not hesitate to contact me or my office.

Sincerely,

Marty J. Jackley
ATTORNEY GENERAL

MJJ/lde

U. S. Department of Justice
Drug Enforcement Administration
8701 Morrissette Drive
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The Honorable Marty J. Jackley
Attorney General
State of South Dakota
1302 East Highway 14
Suite 1
Pierre, South Dakota 57501-8501

Dear Attorney General Jackley:

This responds to your letter to Chuck Rosenberg, Acting Administrator of the Drug Enforcement Administration (DEA) and Robert M. Claiff, Commissioner of the Food and Drug Administration (FDA) dated August 19, 2016, regarding research restrictions involving marijuana and its derivatives, particularly cannabidiol (CBD). The DEA appreciates the opportunity to address your concerns.

As you know, both the DEA and the FDA have statutory roles related to this issue. Both Agencies are fully committed to supporting lawful research involving marijuana and its derivatives, including CBD, while ensuring compliance with the Federal Food, Drug, and Cosmetic Act (FFDCA) and the Controlled Substances Act (CSA). The DEA has taken a number of steps toward that end, which are summarized below.

In December 2015, the DEA adopted a new policy (memorialized in a letter sent to affected registrants and announced on the DEA's website) whereby the DEA waived certain regulatory requirements applicable to those who are conducting research with CBD. Specifically, under this waiver, those conducting clinical trials with CBD no longer have to request approval from the DEA before implementing changes to their research protocols. (A copy of the announcement on the DEA's website and testimony by Joseph T. Rannazzisi before the United States Senate Caucus on International Narcotics Control on June 24, 2015, titled *Cannabidiol: Barriers to Research and Potential Medical Benefits,* are enclosed for your reference.)

On August 12, 2016, the DEA announced in the Federal Register that the Administration has adopted a new policy whereby additional entities may apply to become registered to grow marijuana for the purpose of supplying researchers. (A copy of this document is enclosed for your reference.) As the DEA indicated in the document, the new policy was prompted in large part by the growing interest among some researchers in conducting trials with marijuana extracts that contain a high percentage of CBD – and the corresponding need for additional strains of marijuana in the nation's supply of legally produced material available to researchers.

The DEA is also continuing to assess the current regulatory requirements for conducting research with CBD to determine whether the agency can take further steps to reduce the regulatory burden while continuing to protect the public health and safety.

Finally, the DEA is actively evaluating how best to conduct a scheduling evaluation of CBD in accordance with the CSA scheduling criteria. In carrying out this process, the DEA will be working in close consultation with the FDA.

While the DEA shares your desire to facilitate research with CBD, and to carry out any scheduling actions that are supported by the medical and scientific evidence, as you undoubtedly recognize, the protection of the public health and safety must remain of paramount consideration. Likewise, while we would embrace any decisions by the FDA to approve CBD drugs that have been demonstrated in sound clinical trials to be safe and effective, to date, no drug product containing CBD has yet to be found by the FDA to meet these appropriately rigorous drug approval standards. Despite this, a number of unscrupulous entities have been marketing CBD products in the United States in violation of the FFDCA. The FDA has published on its website some examples of this unlawful conduct, for which it has issued warning letters. See http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm484109.htm and http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm421168.htm.

As the FDA indicates in these announcements, many of the purported "CBD" products being sold to the American public do not contain the chemical ingredients indicated on the labels. Moreover, even a relatively cursory review of purported "CBD" products being sold over the Internet reveals that those who are selling products often make outrageous and dangerous claims about curative properties of the products – such as claiming they can be used to treat various types of cancer.

In sum, the DEA recognizes the possibility that drugs containing CBD might in the future – perhaps even in the near future – be proven to be safe and effective for the treatment of certain conditions and thus approved by the FDA for marketing. Until then, we will continue to strive to make it easier for research to be conducted in this area while never losing sight of the need to protect the public.

I hope this information has been helpful. For information regarding the DEA Diversion Control Division, please visit www.DEAdiversion.usdoj.gov. If you have any additional questions on this issue, please contact the Diversion Control Division Liaison and Policy Section at (202) 307-7297.

Sincerely,

Louis J. Milione
Assistant Administrator
Diversion Control Division

HEADQUARTERS NEWS

December 23, 2015
Contact: DEA Public Affairs
(202) 307-7977

DEA Eases Requirements for FDA-Approved Clinical Trials on Cannabidiol

DEC 23 (WASHINGTON) - The United States Drug Enforcement Administration (DEA) recently eased some of the regulatory requirements imposed by the Controlled Substances Act (CSA) for those who are conducting FDA-approved clinical trials on cannabidiol (CBD), an extract of the marijuana plant. These modifications will streamline the research process regarding CBD's possible medicinal value and help foster ongoing scientific studies. The DEA notified affected researchers by letter of the changes, which take effect immediately.

Federal Regulation (21 CFR 1301.18) requires researchers conducting CBD-based clinical trials under an FDA Investigational New Drug Application to have a DEA research registration. This registration permits the possession of an approved amount of CBD for a specific research protocol. Prior to now, researchers who expanded the scope of their studies and needed more CBD than initially approved for had to request, in writing, a modification to their DEA research registrations – potentially delaying that research while the modification underwent an approval process that includes both the DEA and the Food and Drug Administration (FDA). Under these changes, a previously registered CBD clinical researcher who is granted a waiver can readily modify their protocol and continue their research seamlessly. This waiver effectively removes a step from the approval process.

Marijuana is a Schedule I controlled substance because of the presence of tetrahydrocannabinol (THC), marijuana's psychoactive ingredient. Because CBD contains less than 1 percent THC and has shown some potential medicinal value, there is great interest in studying it for medical applications. Currently, CBD is a Schedule I controlled substance as defined under the CSA. Though the FDA approves drugs for medical use in the United States, the DEA regulates the handling of all controlled substances, including those being used by researchers to conduct studies.

Department of Justice

STATEMENT OF

JOSEPH T. RANNAZZISI
DEPUTY ASSISTANT ADMINISTRATOR
DRUG ENFORCEMENT ADMINISTRATION

BEFORE THE

CAUCUS ON INTERNATIONAL NARCOTICS CONTROL
UNITED STATES SENATE

FOR A HEARING CONCERNING

CANNABIDIOL: BARRIERS TO RESEARCH AND POTENTIAL MEDICAL BENEFITS

PRESENTED

JUNE 24, 2015

Statement of Joseph T. Rannazzisi
Deputy Assistant Administrator
Drug Enforcement Administration
Before the Caucus on International Narcotics Control
United States Senate
June 24, 2015

Good morning Chairman Grassley, Co-Chairman Feinstein, and distinguished Members of the Caucus. I am pleased to speak with you about Drug Enforcement Administration (DEA) regulatory oversight of cannabidiol (CBD) and products containing CBD, and the requirements necessary to conduct research on CBD.

I. Introduction

Under the Controlled Substances Act (CSA), every controlled substance is classified into one of five schedules based upon its potential for abuse, its currently accepted medical use in treatment in the United States, and the degree of dependence the drug or other substance may cause. 21 U.S.C. § 812. The initial schedules of controlled substances established by Congress are found at 21 U.S.C. § 812(c), and the current list of all scheduled substances is published at 21 CFR part 1308. Substances in Schedule I are those that have a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision. 21 U.S.C. 812(b)(1).

Congress placed "marihuana" in Schedule I of the CSA and defined "marihuana" as all parts of the plant *Cannabis sativa L.*, with certain exceptions for the parts of the plant that are not the source of cannabinoids. Among the parts of the cannabis plant included in the definition of marijuana are: the flowering tops, the leaves, viable seeds, and the resin extracted from any part of the plant, and every compound, manufacture, salt, derivative, mixture, or preparation of the plant, its seeds or resin. 21 U.S.C. § 812(c) Schedule I; 21 U.S.C. § 802(16); 21 C.F.R. § 1308.11(d). CBD derived from the cannabis plant is controlled under Schedule I of the CSA because it is a naturally occurring constituent of marijuana. While there is ongoing research into potential medical uses of CBD, at this time CBD has no currently accepted medical use in the United States.

The CSA and the Federal Food, Drug, and Cosmetic Act (FDCA) contain provisions that are specifically designed to allow for both clinical research with, and treatment uses of, investigational drugs, provided certain steps are taken to protect the rights, safety, and welfare of human subjects. The Food and Drug Administration's (FDA) drug approval process, as established by Congress, represents the best way to ensure that safe and effective new medicines are available as soon as possible for the largest numbers of patients.

Currently, there are a number of researchers around the country who are looking into the possible medicinal benefits of CBD. Because no drug products containing CBD are approved for marketing under the FDCA, those wishing to conduct a clinical investigation involving CBD under the FDCA must submit an Investigational New Drug application to the FDA, which must be in effect before any human subject may be enrolled in such investigations.

DEA is committed, consistent with the CSA and the FDCA, to assisting with the healthcare needs of patients. In this regard, the DEA supports research involving CBD and its potential capacity to treat multiple conditions. In June 2014, FDA granted Fast-Track designation to the investigational CBD product, Epidiolex, for study in the treatment of a rare form of childhood epilepsy. FDA has also authorized the use of Epidiolex under Expanded Access, which is designed to facilitate the availability of investigational drug products to patients while those drugs are being studied for approval. DEA supports the use of Expanded Access, which provides access to treatments for patients with serious or immediately life-threatening diseases or conditions, while preserving important protections for those patients. This is a separate process that is available to patients, distinct from the Clinical Trials process. GW Pharmaceuticals, the manufacturer of Epidiolex, has publicly announced that there are over 300 patients being treated through this program, including many pediatric patients with seizure disorders.

DEA will also work with HHS to evaluate CBD under section 201 (a) – (c) of the Controlled Substances Act (21 U.S.C. 811(a-c)). To accomplish this, DEA will initiate the review of CBD and request a scientific and medical evaluation and scheduling recommendation for CBD from HHS. Please be advised, although CBD products are currently being evaluated under Investigational New Drug Applications, additional scientific studies may need to be initiated and conducted to assess CBD's abuse liability. Scheduling recommendations are evidence-based, and DEA will provide any assistance necessary to assist HHS in its collection of information critical to its scientific and medical evaluation and formulation of a recommendation.

II. Current regulations applicable to research involving Schedule I substances

As you know, both DEA and the FDA have statutory roles related to the oversight of research with Schedule I controlled substances such as CBD. DEA understands the importance of supporting the efficient scientific assessment of marijuana and its constituents such as CBD in connection with new drug development. DOJ and DEA are fully committed to supporting lawful research involving marijuana and CBD by ensuring compliance with the Controlled Substances Act and the Single Convention on Narcotic Drugs. DEA will continue to review the relevant regulations to ensure they are consistent with supporting lawful research. If this review

determines that amending the existing regulations governing the Schedule I researcher registration process is necessary to accomplish these goals, DEA would initiate the process to do so. DEA will also continue to work with HHS to streamline the Schedule I Researcher registration process and identify new opportunities for improvement.

A. Registration

The CSA requires:

> Registration applications by practitioners wishing to conduct research with controlled substances in schedule I shall be referred to the Secretary, who shall determine the qualifications and competency of each practitioner requesting registration, as well as the merits of the research protocol. The Secretary, in determining the merits of each research protocol, shall consult with the Attorney General as to effective procedures to adequately safeguard against diversion of such controlled substances from legitimate medical or scientific use. Registration for the purpose of bona fide research with controlled substances in schedule I by a practitioner deemed qualified by the Secretary may be denied by the Attorney General only on a ground specified in section 824(a) of this title.

21 U.S.C. § 823(f).

Section 823(f) provides, in essence, that where a practitioner seeks to conduct research with a Schedule I controlled substance, the respective roles of the agencies are as follows: (1) FDA determines whether the research protocol is scientifically meritorious; and (2) DEA determines whether appropriate safeguards are in place to prevent the diversion of controlled substances and whether the registration would be consistent with 21 U.S.C. § 824(a).

In practice, the researcher submits a research protocol with his or her registration application, which DEA forwards to HHS for review. Once HHS determines that the researcher is qualified and the research protocol is scientifically meritorious, DEA will grant the registration, provided the researcher will have in place effective controls against the diversion of controlled substances, and the circumstances do not warrant a denial pursuant to 21 U.S.C. 824(a) (e.g., the applicant has not materially falsified the application, the applicant has not been convicted of a controlled substance-related felony).

To date, DEA has not denied any research application that has met the CSA requirements. In fact, the number of authorized Schedule I researchers, including CBD researchers, continues to grow.[1] Between November 2014 and June 4, 2015, the number of

[1] As of November 17, 2014, there were approximately 237 active Schedule I researchers registered with DEA. Of those 237,166 were approved to perform bona fide research with marijuana, marijuana extracts, and marijuana

researchers approved to conduct research with CBD on human subjects has increased from 16 to 41. As of June 4, 2015, there are 399 active researchers registered with the DEA to conduct bona fide research with Schedule I controlled substances. Of these 399 Schedule I researchers, 265 active researchers are registered with DEA to conduct bona fide research with marijuana and marijuana extracts that include CBD, and 41 researchers are approved to conduct research with CBD on human subjects. Each of these 41 researchers is approved to conduct or supervise an investigation with at least one study subject if not more with synthetic or plant-derived CBD. In furtherance of our ongoing efforts to support CBD research, DEA will continue its policy of expediting these applications.

B. Amended Schedule I Protocols

Under current DEA regulations, when a researcher who is in the midst of an ongoing, approved study seeks to increase the quantity of the Schedule I controlled substance being used for the research, the researcher must submit to DEA an amendment to the approved protocol. 21 C.F.R. § 1301.18(c). "Upon return of the receipt, the registrant shall be authorized to purchase the additional quantity of the controlled substance or substances specified in the request." *Id.* DEA forwards this information to HHS, and HHS "shall approve or deny the request as an amendment to the protocol." *Id.* Submission of an amendment does not stop research with the previously approved protocol, which remains active. The researcher may continue to conduct research pursuant to the previously approved protocol.

DEA's role in the process is to ensure that there is accurate accounting and security for the increase in material. From a diversion control standpoint, DEA needs to be informed of any changes in the quantity of Schedule I drug to ensure that there continue to be effective procedures to guard against diversion of all such controlled substance material. Further, in some instances, the Schedule I drug that is used in the clinical trial is imported. In such cases, where the researcher seeks to use more material than indicated in the original protocol, 21 C.F.R. § 1301.18(c) allows the increased amounts to be legitimately used in research, thereby providing the basis for allowing the increased amount to be imported pursuant to 21 U.S.C. § 952(a)(2)(C) (authorizing the import of Schedule I substances if in limited quantities for research uses).

The quantity changes might impact the scientific merit of the research; therefore, the regulations require the researcher to provide to DEA and FDA notice of the additional quantities of controlled substances that the researcher wishes to procure. FDA reviews the proposed

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derivatives such as CBD and cannabinol. Of these, 16 researchers were approved to conduct research with CBD on human subjects. As of February 25, 2015, there were 372 active researchers registered with the DEA to conduct bona fide research with Schedule I controlled substances. Of these 372 researchers, 247 active researchers were registered to conduct bona fide research with marijuana and marijuana extracts that include CBD. As of June 4, 2015, there were 399 active researchers registered with the DEA to conduct bona fide research with Schedule I controlled substances; of these 399 researchers, 265 active researchers were registered to conduct bona fide research with marijuana and marijuana extracts.

increase in quantity to ensure that the protocol remains scientifically sound and meritorious, and safe for human research subjects.

C. Supplemental Schedule I Protocols

If an approved researcher intends to deviate from the previously approved research protocol other than in the quantity of controlled substance (e.g., if a researcher were to seek to expand the subject group to include pediatric patients, to include patients with different diagnoses or suffering from life-threatening ailments, or to change the method of delivery of the drug), the researcher must submit a supplemental protocol to DEA. DEA forwards the supplemental protocol to FDA for review and approval. These types of changes might raise significant new questions concerning the scientific merits of the protocol. Close review is important because material deviations in the research protocol could potentially alter the scientific merit of the research and have impacts on the health and safety of the human research subjects. For this reason, protocol changes noted in 21 C.F.R. § 1301.18(d) – unlike the quantity changes in 21 C.F.R. § 1301.18(c) – are reviewed in the same manner as an original protocol. The Schedule I researcher may continue research using the previously approved protocol until DEA and FDA take the final action regarding the supplemental protocol.

D. Processing Timeframes

It is important to act expeditiously on applications for Schedule I research. The timeframes for DEA's and FDA's processing of Schedule I research applications are specified in the regulations. DEA forwards complete Schedule I research protocols to the FDA within seven days of receipt; FDA notifies DEA of its determination regarding the merits of the protocol within 30 days; and DEA issues a certificate within 10 days of receiving the FDA's notice. 21 C.F.R. 1301.32(c). It should be noted that although many clinical researchers may be subject to a standardized protocol, thereby streamlining the process, some researchers must also meet institutional and State requirements prior to approval. DEA works closely with researchers to assist with the expeditious completion of their protocol submission and registration application.

III. Conclusion

The CSA allows for bona fide research with Schedule I controlled substances, provided that FDA has determined the researcher to be qualified and competent and the research protocol to be meritorious. Researchers who meet these criteria, as well as the other criteria set forth in the CSA, may obtain a registration to conduct research with a Schedule I controlled substance.

DEA is committed, consistent with the CSA and the FDCA, to assisting the health care needs of patients and supporting research involving CBD. DEA shares the view that medical

decisions should be based on science and adherence to established drug approval processes. Accordingly, DEA will continue to make the review and approval of Schedule I researchers a top priority, and will make every effort to ensure that research continues where CSA requirements are met.

I look forward to taking your questions.

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1301

[Docket No. DEA–447]

Applications To Become Registered Under the Controlled Substances Act To Manufacture Marijuana To Supply Researchers in the United States

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Policy statement.

SUMMARY: To facilitate research involving marijuana and its chemical constituents, DEA is adopting a new policy that is designed to increase the number of entities registered under the Controlled Substances Act (CSA) to grow (manufacture) marijuana to supply legitimate researchers in the United States. This policy statement explains how DEA will evaluate applications for such registration consistent with the CSA and the obligations of the United States under the applicable international drug control treaty.

DATES: August 12, 2016.

FOR FURTHER INFORMATION CONTACT: Michael J. Lewis, Office of Diversion Control, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (202) 598–6812.

SUPPLEMENTARY INFORMATION:

Background

Reasons for This Policy Statement

There is growing public interest in exploring the possibility that marijuana or its chemical constituents may be used as potential treatments for certain medical conditions. The Federal Food, Drug and Cosmetic Act requires that before a new drug is allowed to enter the U.S. market, it must be demonstrated through adequate and well-controlled clinical trials to be both safe and effective for its intended uses. Congress long ago established this process, recognizing that it was essential to protect the health and welfare of the American people.

Although no drug product made from marijuana has yet been shown to be safe and effective in such clinical trials, DEA—along with the Food and Drug Administration (FDA) and the National Institutes of Health (NIH)—fully supports expanding research into the potential medical utility of marijuana and its chemical constituents.[1]

There are a variety of factors that influence whether and to what extent such research takes place. Some of the key factors—such as funding—are beyond DEA's control.[2] However, one of the ways DEA can help to facilitate research involving marijuana is to take steps, within the framework of the CSA and U.S. treaty obligations, to increase the lawful supply of marijuana available to researchers.

For nearly 50 years, the United States has relied on a single grower to produce marijuana used in research. This grower operates under a contract with the National Institute on Drug Abuse (NIDA). This longstanding arrangement has historically been considered by the U.S. Government to be the best way to satisfy our nation's obligations under the applicable international drug control treaty, as discussed in more detail below. For most of the nearly 50 years that this single marijuana grower arrangement has been in existence, the demand for research-grade marijuana in the United States was relatively limited—and the single grower was able to meet such limited demand. However, in recent years, there has been greater public interest in expanding marijuana-related research, particularly with regard to certain chemical constituents in the plant known as cannabinoids.

The term "cannabinoids" generally refers to those chemicals unique to the cannabis plant (marijuana).[3] To date, more than 100 different cannabinoids have been found in the plant. One such cannabinoid—known as cannabidiol or CBD—has received increased attention in recent years. Although the effects of CBD are not yet fully understood by scientists, and research is ongoing in this area, some studies suggest that CBD may have uses in the treatment of seizures and other neurological disorders. A growing number of researchers have expressed interest in conducting research with extracts of marijuana that have a particular percentage of CBD and other cannabinoids. DEA fully supports research in this area. Based on discussions with NIDA and FDA, DEA has concluded that the best way to satisfy the current researcher demand for a variety of strains of marijuana and cannabinoid extracts is to increase the number of federally authorized marijuana growers. To achieve this result, DEA, in consultation with NIDA and FDA, has developed a new approach to allow additional marijuana growers to apply to become registered with DEA, while upholding U.S. treaty obligations and the CSA. This policy statement explains the new approach, provides details about the process by which potential growers may apply for a DEA registration, and describes the steps they must take to ensure their activity will be carried out in conformity with U.S. treaty obligations and the CSA.

The historical system, under which NIDA relied on one grower to supply marijuana on a contract basis, was designed primarily to supply marijuana for use in federally funded research—not for commercial product development. Thus, under the historical system, there was no clear legal pathway for commercial enterprises to produce marijuana for product development. In contrast, under the new approach explained in this policy statement, persons may become registered with DEA to grow marijuana not only to supply federally funded or other academic researchers, but also for strictly commercial endeavors funded by the private sector and aimed at drug product development. Likewise, under the new approach, should the state of scientific knowledge advance in the future such that a marijuana-derived drug is shown to be safe and effective for medical use, pharmaceutical firms will have a legal means of producing such drugs in the United States—independent of the NIDA contract process.

Legal Considerations

Applicable CSA Provisions

Under the CSA, all persons who seek to manufacture or distribute a controlled substance must apply for a DEA registration. 21 U.S.C. 822(a)(1). Applications by persons seeking to grow

[1] There are two FDA-approved drugs that contain a synthetic form of dronabinol, which is one of the chemicals found in marijuana. These drugs are Marinol (which the FDA approved for the treatment of nausea and vomiting associated with cancer chemotherapy, and for the treatment of anorexia associated with weight loss in patients with AIDS) and Syndros (which was approved for the same indications as Marinol).

[2] Funding may actually be the most important factor in whether research with marijuana (or any other experimental drug) takes place. What appears to have been the greatest spike in marijuana research in the United States occurred shortly after the State of California enacted legislation in 1999 to fund such research. Specifically, in 1999, California enacted a law that established the "California Marijuana Research Program" to develop and conduct studies on the potential medical utility of marijuana. Cal. Health & Safety Code § 11362.9. The state legislature appropriated a total of $9 million for the marijuana research studies. Over the next five years, DEA received applications for registration in connection with at least 17 State-sponsored pre-clinical or clinical studies of marijuana (all of which DEA granted). 74 FR 2101, 2105 (2009). However, it appears that once the State stopped funding the research, the studies ended.

[3] An acceptable and broader definition of "cannabinoids" includes not only those chemicals unique to the cannabis plant but also their derivatives and transformation products.

marijuana to supply researchers are governed by 21 U.S.C. 823(a); *see generally* 76 FR 51403 (2011); 74 FR 2101 (2009). Under section 823(a), for DEA to grant a registration, two conditions must be satisfied: (1) The registration must be consistent with the public interest (based on the enumerated criteria listed in section 823(a)) and (2) the registration must be consistent with U.S. obligations under the Single Convention on Narcotic Drugs, 1961 (Single Convention). An applicant seeking registration under section 823(a) has "the burden of proving that the requirements for such registration pursuant to [this section] are satisfied." 21 CFR 1301.44(a). Although each application for registration that DEA receives will be evaluated individually based on its own merit, some general considerations warrant mention here.

First, while it is DEA's intention to increase the number of registered marijuana growers who will be supplying U.S. researchers, the CSA does not authorize DEA to register an unlimited number of manufacturers. As subsection 823(a)(1) provides, DEA is obligated to register only the number of bulk manufacturers of a given schedule I or II controlled substance that is necessary to "produce an adequate and uninterrupted supply of these substances under adequately competitive conditions for legitimate medical, scientific, research, and industrial purposes." *See* 74 FR at 2127–2130 (discussing meaning of subsection 823(a)(1)). This provision is based on the long-established principle that having fewer registrants of a given controlled substances tends to decrease the likelihood of diversion.

Consistent with subsection 823(a)(1), DEA will evaluate each application it receives to determine whether adding such applicant to the list of registered growers is necessary to provide an adequate and uninterrupted supply of marijuana (including extracts and other derivatives thereof) to researchers in the United States.[4]

Second, as with any application submitted pursuant to section 823(a), in determining whether the proposed registration would be consistent with the public interest, among the factors to be considered are whether the applicant has previous experience handling controlled substances in a lawful manner and whether the applicant has engaged in illegal activity involving controlled substances. In this context, illegal activity includes any activity in violation of the CSA (regardless of whether such activity is permissible under State law) as well as activity in violation of State or local law. While past illegal conduct involving controlled substances does not automatically disqualify an applicant, it may weigh heavily against granting the registration.

Third, given the in-depth nature of the analysis that the CSA requires DEA to conduct in evaluating these applications, applicants should anticipate that, in addition to the information requested in the application itself, they will be asked to submit other information germane to the application in accordance with 21 CFR 1301.15. This will include, among other things, detailed information regarding an applicant's past experience in the manufacture of controlled substances. In addition, applicants will be asked to provide a written explanation of how they believe they would be able to augment the nation's supply of research-grade marijuana within the meaning of subsection 823(a)(1). Applicants may be asked to provide additional written support for their application and other information that DEA deems relevant in evaluating the application under section 823(a).

Treaty Considerations

As stated above, DEA may only issue a registration to grow marijuana to supply researchers if the registration is consistent with U.S. obligations under the Single Convention. Although this policy document will not list all of the applicable requirements of the Single Convention,[5] the following is a summary of some of the key considerations.

Under articles 23 and 28 of the Single Convention, a party (*i.e.*, a country that is a signatory to the treaty) that allows the cultivation of cannabis for lawful uses (*e.g.*, FDA-authorized clinical trials) must:

(a) Designate the areas in which, and the plots of land on which, cultivation of the cannabis plant for the purpose of producing cannabis shall be permitted;

(b) License cultivators authorized to cultivate cannabis;

(c) Specify through such licensing the extent of the land on which the cultivation is permitted;

(d) Purchase and take physical possession of all cannabis crops from all cultivators as soon as possible, but not later than four months after the end of the harvest; and

(e) Have the exclusive right of importing, exporting, wholesale trading and maintaining stocks of cannabis.

As DEA has stated in a prior publication, DEA carries out those functions of article 23, paragraph 2, that are encompassed by the DEA registration system (paragraphs (a) through (c) above), and NIDA carries out those functions relating to purchasing the marijuana and maintaining a monopoly over the wholesale distribution (paragraphs (d) and (e) above).[6] 76 FR at 51409.

As indicated, DEA's historical approach to ensuring compliance with the foregoing treaty requirements was to limit the registration of marijuana growers who supply researchers to those entities that operate under a contract with NIDA. Under this historical approach, the grower could be considered an extension of NIDA and thus all marijuana produced by the grower was effectively owned by NIDA, with NIDA controlling all distribution to researchers.

However, as further indicated, DEA has concluded, based on discussions with NIDA and FDA, that it would be beneficial for research to allow additional marijuana growers outside the NIDA-contract system, provided this could be accomplished in a manner consistent with the CSA and the treaty. Toward this end, DEA took into account the following statement contained in the official commentary to the Single Convention:

> Countries . . . which produce . . . cannabis . . . , [i]n so far as they permit private farmers to cultivate the plants . . . , cannot establish with sufficient exactitude the quantities harvested by individual producers. If they allowed the sale of the crops to private traders, they would not be in a position to ascertain with reasonable exactitude the amounts which enter their controlled trade. The effectiveness of their control régime would thus be considerably weakened. In fact, experience has shown that permitting licensed private traders to purchase the crops results in diversion of large quantities of drugs into illicit channels. . . . [T]he acquisition of the crops and the wholesale and international trade in these agricultural products cannot be entrusted to private traders, but must be undertaken by governmental authorities in the producing countries. Article 23 . . . and article 28 . . . therefore require a government monopoly of the wholesale and international trade in the agricultural product in question in the country which authorizes its production.
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> Commentary at 278

[4] In making this determination, DEA will consult with NIH and FDA, as warranted.

[5] A detailed explanation of the relevant Single Convention requirements can be found in 74 FR at 2114–2118.

[6] In accordance with the CSA, DEA carries out functions that are indirectly related to those specified in article 23, paragraph 2(e). For example, DEA controls imports and exports of cannabis through the CSA registration and permitting system.

Given the foregoing considerations, DEA believes it would be consistent with the purposes of articles 23 and 28 of the Single Convention for DEA to register marijuana growers outside of the NIDA-contract system to supply researchers, *provided the growers agree that they may only distribute marijuana with prior, written approval from DEA.* In other words, in lieu of requiring the growers to operate under a contract with NIDA, a registered grower will be permitted to operate independently, provided the grower agrees (through a written memorandum of agreement with DEA) that it will only distribute marijuana with prior, written approval from DEA. DEA believes this new approach will succeed in avoiding one of the scenarios the treaty is designed to prevent: Private parties trading in marijuana outside the supervision or direction of the federal government.

Also, consistent with the purposes and structure of the CSA, persons who become registered to grow marijuana to supply researchers will only be authorized to supply DEA-registered researchers whose protocols have been determined by the Department of Health and Human Services (HHS) to be scientifically meritorious. *See* 21 U.S.C. 823(f). In 2015, HHS announced the details of its current policy for evaluating the merits of research protocols involving marijuana. 80 FR 35960 (2015).

Finally, potential applicants should note that any entity granted a registration to manufacture marijuana to supply researchers will be subject to all applicable requirements of the CSA and DEA regulations, including those relating to quotas, record keeping, order forms, security, and diversion control.

How To Apply for a Registration

Persons interested in applying for a registration to become a bulk manufacturer of marijuana to supply legitimate researchers can find instructions and the application form by going to the DEA Office of Diversion Control Web site registration page at *www.deadiversion.usdoj.gov/drugreg/index.html#regapps.* Applicants will need to submit Form 225.

Note Regarding the Nature of This Document

This document is a general statement of DEA policy. While this document reflects how DEA intends to implement the relevant statutory and regulatory provisions, it does not establish a rule that is binding on any member of the public. Any person who applies for a registration to grow marijuana (as with any other applicant for registration under the CSA) is entitled to due process in the consideration of the application by the Agency. To ensure such due process, the CSA provides that, before taking action to deny an application for registration, DEA must serve upon the applicant an order to show cause why the application should not be denied, which shall provide the applicant with an opportunity to request a hearing on the application in accordance with the Administrative Procedure Act. 21 U.S.C. 824(c).

Dated: July 25, 2016.

Chuck Rosenberg,

Acting Administrator.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Marty J. Jackley
Attorney General
State of South Dakota
1302 East Highway 14, Suite 1
Pierre, South Dakota 57501-8501

Dear Attorney General Jackley:

Thank you for your letter of August 19, 2016, addressed to Commissioner Califf regarding the development of therapies derived from marijuana and its constituents. Your letter was forwarded to me for response.

The U.S. Food and Drug Administration (FDA) shares your concern for children and adults suffering from diseases such as epilepsy and cancer, and is committed to advancing the development of new therapies. We agree that the drug approval process represents the best way to help ensure that any medicines derived from cannabidiol (CBD) or other constituents of marijuana are appropriately reviewed for safety and effectiveness, consistent with FDA's statutory requirements. It is important and appropriate to use the same scientific standards in the development and assessment of potential therapeutic uses of cannabidiol as with any unapproved drug the Agency reviews.

At present, FDA has approved several drugs for human use which contain active ingredients that are present, or similar to those present, in botanical marijuana. FDA approved Marinol capsules in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who had failed to respond adequately to conventional antiemetic treatments. Marinol capsules include the active ingredient dronabinol, a synthetic delta-9-tetrahydrocannabinol, or THC, which is a psychoactive component of marijuana. Marinol capsules also were approved in 1992 for the treatment of anorexia associated with weight loss in patients with AIDS. In addition, FDA recently approved Syndros, a dronabinol oral solution, for the same indications as Marinol. And finally, FDA approved Cesamet capsules for the treatment of nausea and vomiting associated with chemotherapy in 1985. Cesamet capsules contain the synthetic cannabinoid nabilone as the active ingredient.

FDA has not, as of now, approved any drug containing marijuana or CBD as safe and effective for any therapeutic use. FDA is working diligently to support scientific studies that may determine the safety and effectiveness of these products. Development programs for drugs derived from marijuana may be eligible for expedited review and development programs[1] under appropriate circumstances, and some of these expedited review pathways are being used to aid the development or review of drugs derived from marijuana. For example, in April 2014, GW

[1] FDA has several programs that directly facilitate and expedite development and review of new drugs that address unmet medical needs in the treatment of serious or life-threatening conditions: fast track, accelerated approval, priority review, and breakthrough therapy designation.

Pharmaceuticals announced that FDA granted fast track designation to its investigational drug product Sativex "for the treatment of pain in patients with advanced cancer, who experience inadequate analgesia during optimized chronic opioid therapy."[2] According to GW Pharmaceuticals, "Sativex is an investigational product composed primarily of two cannabinoids: CBD and THC, administered as a metered-dose oromucosal spray."[3] In addition, on June 6, 2014, GW Pharmaceuticals announced that FDA granted Fast Track designation to its investigational CBD product, Epidiolex, "in the treatment of Dravet syndrome, a rare and catastrophic treatment-resistant form of childhood epilepsy."[4] In February 2015, Insys Therapeutics announced that FDA granted Fast Track designation to "its pharmaceutical cannabidiol for the treatment of Dravet syndrome."[5]

To encourage appropriate research into marijuana and its constituents, FDA has also worked with investigators to provide clear information on how to conduct research in this area. To help address common questions about research into marijuana, FDA, the National Institute on Drug Abuse (NIDA), and the Drug Enforcement Administration (DEA) all have created online materials to help researchers.[6] We also know that a number of states are interested in allowing access to cannabinoid oil, or CBD, to treat childhood epilepsy. FDA encourages and supports medical research into the safety and effectiveness of marijuana products through adequate and well-controlled clinical trials conducted under an appropriate investigational new drug application (IND) and consistent with DEA requirements for research on Schedule I substances. FDA has provided scientific advice to representatives from several states considering support for medical research of marijuana and its derivatives, including CBD, to help ensure that their research is rigorous and appropriate.

Please be assured that FDA is committed to providing timely access to potentially useful treatments for seriously ill patients, and to working with pharmaceutical companies to facilitate research and the development of new drugs. FDA has a long-standing commitment to encouraging the development of new treatments for serious and life-threatening diseases, and will continue to apply its expedited programs authority – including accelerated approval – to any marijuana-derived therapies that meet the relevant criteria.[7]

Thank you for your interest in this matter.

Sincerely,

B. T. Kehoe

Brian T. Kehoe
Director of Intergovernmental Affairs

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[2] http://www.gwpharm.com/GW%20Pharmaceuticals%20Announces%20that%20Sativex%20Receives%20Fast%20Track%20Designation%20from%20FDA%20in%20Cancer%20Pain.aspx.

[3] Id.

[4] http://www.gwpharm.com/GW%20Pharmaceuticals%20Announces%20Epidiolex%20Receives%20Fast%20Track%20Designation%20from%20FDA%20for%20the%20Treatment%20of%20Dravet%20Syndrome.aspx.

[5] http://investors.insysrx.com/phoenix.zhtml?c=115949&p=irol-newsArticle&ID=2033632.

[6] http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/ucm362986.htm;
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf;
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070491.pdf;
http://www.drugabuse.gov/drugs-abuse/marijuana/marijuana-research-nida;
http://www.deadiversion.usdoj.gov/drugreg/faq.htm#sched1.

[7] See http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf