May 22, 2020

Mr. Scott A. Brinks  
Regulatory Drafting and Policy Support Section (DPW)  
Diversion Control Division  
Drug Enforcement Administration  
8701 Morrissette Drive  
Springfield, VA 22152–2639

Dear Mr. Brinks:

The American Psychological Association (APA) and the College on Problems of Drug Dependence (CPDD) appreciate the opportunity to respond to the Notice of Proposed Rule Making (NPRM) [RIN 1117-AB54/Docket No. DEA-506], “Controls to Enhance the Cultivation of Marihuana for Research in the United States.”

Our organizations were pleased to see the interest generated by the August 12, 2016, notice “Applications to Become Registered under the Controlled Substances Act to Manufacture Marijuana to Supply Researchers in the United States, 81 FR 53846” and we appreciate DEA’s careful review of the Controlled Substances Act (CSA), including the provisions requiring consistency with obligations under international treaties such as the Single Convention on Narcotic Drugs (detailed in articles 23 and 28) and the changes to the 2016 policy described below. We wholeheartedly agree with the intent of the NPRM as described by DEA, which “believes that these changes will enhance and improve research with marihuana and facilitate research that could result in the development of marihuana-based medicines approved by the Food and Drug Administration (FDA).”

The Market for Research Grade Cannabis in NIH-Funded Studies is Small
The NPRM indicates that based on approximately 35 pending applications, the applicant pool of suppliers of research grade cannabis can be divided into three categories: “(1) A Bulk Manufacturer Who Grows Marihuana for Its Own Research or Drug Development Purposes; (2) A Bulk Manufacturer Who Supplies Marihuana to Other DEA Registrants, Including National Institutes of Health Funded and Non-National Institutes of Health Funded Researchers; and (3) A Bulk Manufacturer Who Supplies Marihuana To Support NIDA’s Drug Supply Program (DSP).”
We are not privy to the distribution of the applications across those three groups but recognize from the section titled Regulatory Analyses (Affected Number of Small Entities) that the research market for the second and third categories is very small. By DEA’s own calculation “DEA estimates 40 researchers are affected by this proposed rule. The 40 researchers represent the approximate number of researchers that receive marihuana from NIDA’s marihuana DSP.” Further, the National Institute on Drug Abuse (NIDA) DSP only distributed, in total, 16 lbs. of botanical cannabis for research in 2019 (personal communication, Dr. Richard Kline, Chemical and Pharmaceutical Branch Chief at NIDA).

One overarching concern we have is that manufacturers in categories 2 and 3 will need to be highly motivated to supply that small market. We urge DEA to minimize bureaucratic regulatory hurdles that might serve to discourage both new and established manufacturers in these categories.

**Real World Products: Quality Control and the Public Interest**

Both APA and CPDD have articulated the need for a broader range of cannabinoid products that more closely reflect those available in state dispensaries. Even if approved applicants begin to manufacture those products, it seems unlikely that there will be a surge in the pool of extramural scientists studying these Schedule I cannabinoids because of the real and perceived regulatory burdens imposed on Schedule I registrants. Thus, the market will remain small for the foreseeable future and it will be critical not to disadvantage, disenfranchise, or disincentivize applicants who are willing to produce products for that extramural research market.

With that in mind, we are concerned about how DEA will interpret the Application of Public Interest Factors outlined in Part C of the Background and Purpose of This Proposed Rule. DEA states that “the proposed rule would explain how DEA will evaluate whether a particular application is consistent with the public interest factors of 21 U.S.C. 823(a), including factor 823(a)(1).” The NPRM “…further provides that the Administrator’s determination of which applicants to select will be consistent with the public interest factors in section 823(a), …with particular emphasis on the criteria discussed in the preceding paragraph as well as the following: (1) The applicant’s ability to consistently produce and supply marihuana of a high quality and defined chemical composition; and (2) Whether the applicant has demonstrated prior compliance with the CSA and DEA regulations.”

We strongly endorse the first of these two factors. It is essential that any botanical cannabis, “medicinal cannabis,” or “cannabis preparations” be cultivated and processed in accordance with Current Good Manufacturing Practices and all applicable Chemical Manufacturing and Controls (CMC) guidance as set forth by the Food and Drug Administration (FDA) including testing for heavy metals, aflatoxins, pesticides and microbial contamination. Further, we recommend that DEA hold applicants to a two-stage process that provides for a demonstrated
proof of concept with a small-scale build-out to ensure they are capable of manufacturing research grade products as a condition of registration.

We believe the second factor should be evaluated in the context of the broader sense of “public interest.” It is indisputable that facilitating more research on cannabinoids will benefit public health and the public interest. Unfortunately, the applicants most likely to provide consistent, high-quality products for research already have experience manufacturing cannabis products, but by virtue of that experience they have not complied with CSA and DEA regulations. We recommend that DEA change the second factor to: 2) The applicant will demonstrate compliance with the CSA and DEA regulations.

The NPRM indicates that DEA will have the exclusive right of importing, exporting, wholesale trading, and maintaining cannabis stocks to comply with the Single Convention. This raises the possibility of inefficiencies and expenses that may severely limit the ability to do research. For instance, it is proposed that DEA may take possession of crops grown by manufacturers and redistribute the product. Instead, we recommend that manufactured crops be stored at, and redistributed from, the manufacturing site to avoid adding time and expense to providing cannabis products to scientists in the field. Further, wherever the crop is stored, DEA must ensure that the appropriate CMC testing is in place to guarantee the stability of all products. This CMC information must be readily available to investigators for FDA Investigational New Drug applications.

Lastly, the NPRM assumes that National Institutes of Health (NIH) funding will pay for the purchase of research marijuana products by NIH grantees and notes that “Marihuana is also available to research investigators who are funded through non-federal sources. Although NIDA considered charging for marihuana on a ‘cost-reimbursement basis,’ the current policy is to provide the marihuana at ‘no charge’.” We believe that neither NIH nor the investigators should bear any additional costs for acquisition, testing, storage, or distribution of cannabis, medicinal cannabis, or cannabis preparations associated with a new custodial system of DEA’s design.

**Beyond the NPRM: Additional Actions Needed to Facilitate Cannabis Research**

Making a wider range of cannabinoid products available for research is only part of the solution. We need more scientists conducting research on cannabinoids and that will require a wholesale re-evaluation of DEA’s role in oversight of cannabinoid research. DEA cites an overarching need to maintain consistency with international treaty obligations in its approach to regulating research with Schedule 1 controlled substances. However, satisfying those obligations does not require the elaborate security requirements codified in the CSA for cannabis research given the history of good stewardship by scientist registrants and the widespread availability of illicit cannabis.
Scientists are responsible stewards of pharmaceutical compounds scheduled under the CSA as evidenced by the lack of DEA enforcement actions against registrants with Ph.D. degrees. As shown on the DEA’s Diversion Control Division website, a detailed list spanning twenty years of criminal cases against hundreds of individuals with doctoral level degrees (who also include physicians, veterinarians, osteopaths, nurse practitioners, pharmacists, and other allied health professionals) indicates only one action was filed against an individual with a Ph.D., a plant biologist. The majority of criminal actions prosecuted by DEA appear to involve physicians and allied health professionals who have diverted Schedule II-V drugs that they had access to in their professional settings.

Scientists receive special training in the ethical and responsible conduct of research and invest extraordinary time, effort, and expense to gain credibility within the research community. They know that even an unintentional violation of DEA protocols could easily damage their careers. It takes an average of 7.3 years for scientists to obtain a research degree after starting graduate school and Ph.D. scientists receiving their first independent Research Project Grant from NIH are on average 43 years old.

In order to facilitate more research, DEA could enact specific research exceptions for cannabinoids for the regulatory framework currently in place for Schedule I compounds (i.e. levels of security, protocol review, and protocol amendment). That would markedly decrease the burden, and current raft of disincentives, imposed on scientists interested in pursuing careers in cannabinoid research. Relaxing the regulatory framework also makes sense given the wide availability of cannabis in the US. DEA’s own evaluation of the most recent eight factor analysis in support of maintaining cannabis in Schedule I, includes the following:

“The HHS stated that there is a lack of significant diversion from legitimate drug sources, but that this is likely due to high availability of marijuana from illicit sources...marijuana is the most commonly used illegal drug in the United States. It is also the most commonly used illicit drug by American high schoolers. Marijuana is the most frequently identified drug in state, local, and federal forensic laboratories, with increasing amounts of both domestically grown and of illicitly smuggled marijuana. Given that marijuana has long been the most widely trafficked and abused controlled substance in the United States, and that all aspects of such illicit activity are entirely outside of the closed system of distribution mandated by the CSA, it may well be the case that there is little thought given to diverting marijuana from the small supplies produced for legitimate research purposes.”(Bolding added)

The Role of DEA in Context: Diversion, Science, and Safety
While there is no evidence of diversion by malfeasance of registrants, even if 100% of the 2019 DEA Aggregate Production Quota of cannabis allowed to be grown for research (5,400 lbs.)
were to be diverted by theft, that would make up 0.022% of the estimated illicit domestically produced cannabis available on the **black market** (24,400,000 lbs.) in 2019. In addition, last year, NIDA only distributed, in total, 16 lbs. of cannabis for research (personal communication, Dr. Richard Kline, Chemical and Pharmaceutical Branch Chief at NIDA). So, all the infrastructure, security, and protocol review (see Appendix) was in place to safeguard just 16 lbs. of cannabis.

Further, there is little rationale for DEA to be involved in scientific protocol review for cannabis research, which is adequately and, arguably, better handled by Institutional Review Boards and the FDA. Scientific review lies outside of the scope of DEA’s role as an arm of the Department of Justice and adds significant delays for scientists seeking to initiate or modify cannabis research protocols. This is particularly troubling for junior scientists who must demonstrate significant progress early in their careers. The time it takes for registration and approval of Schedule I protocols serves as a strong disincentive for early career scientists to pursue research on cannabinoids.

Cannabis has proved to be a relatively safe drug to administer in research laboratories and the toxic effects of high dose cannabis administration resolve with time as the active constituents are metabolized. Although withdrawal from long term cannabis use can result in anxiety, irritability, cannabis craving, restlessness, sleep disturbances and appetite suppression, those effects manifest within 24 hours and typically resolve within 1 to 2 weeks. There has never been a recorded case of cannabis overdose resulting in death. By comparison, alcohol, another pharmacologically active substance used recreationally by millions across the US (and which has no approved medicinal use), is lethal when used at high doses acutely, is **increasingly implicated in chronic morbidity and mortality**, and can cause life threatening seizures upon withdrawal in alcohol dependent individuals.

In closing, we thank the DEA for the opportunity to comment on this important NPRM and the leap forward it represents for cannabinoid research. It is critical that cannabinoid research catch up with the real world use of this class of compounds in order to better understand their potential harms and develop more effective treatments for cannabis use disorder as well as to unlock the potential therapeutic uses of cannabinoids in treating a variety of medical conditions. The American Psychological Association and College on Problems of Drug Dependence would be pleased to lend the expertise of our memberships to facilitate progress in this area as this initiative matures.

Please contact Dr. Geoffrey Mumford, Senior Director for Science Policy, APA Science Directorate, at gmumford@apa.org or (202) 336-6067, or Dr. Sandra Comer, CPDD Public Policy Officer, at sdc10@cumc.columbia.edu or (917) 273-2420, should you have any questions.
Jaime L. Diaz-Granados, PhD
Deputy Chief Executive Officer
Acting Chief Scientific Officer
American Psychological Association

Elise Weerts, PhD
President, The College on Problems of Drug Dependence
APPENDIX
Flow charts depicting the complexity of the current regulatory framework for conducting research with cannabinoids

CONDUCTING CLINICAL RESEARCH ON MARIJUANA

Develop Research Proposal
[2-3 months]

IRB Review & Approval
[2-3 months]

IND Review & Approval (FDA)
[1 month min]

State Schedule I Registration
Verify Protocol
Background Check
Site Inspection
Annual renewals
[2-4 months]

Federal Schedule I Registration
Protocol Review (DEA/FDA)
Background Check (DEA)
Site Inspection (DEA)
Annual Renewals
[3-6 months or more]

NIDA Drug Supply Program
Confirms IRB and IND approvals, protocol review, & federal registration.
[Marijuana shipped 3-4 weeks after order submission]

Protocol Changes
[Research stops while amending protocols]
Amend IRB Approval
Amend IND
Revise State Registration
Revise Federal Registration
Resume Research

Review Scientific Protocol
Federally Funded
Federal Grant Review/Funding
Grant Submission
Peer Review
Advisory Council Review
Director Approval
[~9 months]

Non-Federally Funded
Protocol Review
By external scientific experts
[Coordinated by NIDA]
[1-2 months]
CONDUCTING BASIC RESEARCH ON MARIJUANA

Develop Research Proposal (2-3 months)

IACUC Review & Approval (1-2 months)

Review Scientific Protocol
- Federally Funded
  - Federal Grant Review/Funding
    - Grant Submission
    - Peer Review
    - Advisory Council Review
    - Director Approval
    - (≈9 months)
- Non-Federally Funded
  - Protocol Review
    - By external scientific experts
    - (Coordinated by NIDA)
    - (1-2 months)

Protocol Changes
- Research stops while amending protocols
  - Amend IACUC Approval
  - Revise State Registration
  - Revise Federal Registration
  - Resume Research

State Schedule I Registration
- Verify Protocol
- Background Check
- Site Inspection
- Annual renewals
  - [2-4 months]

Federal Schedule I Registration
- Protocol Review (DEA/FDA)
- Background Check (DEA)
- Site Inspection (DEA)
- Annual Renewals
  - [3-6 months or more]

NIDA Drug Supply Program
- Confirms IACUC approval, protocol review, & federal license.
  - (Marijuana ships ~3-4 weeks after order submission)