APR 4 2016

Thank you for your December 21, 2015, letter. We hope that you will find the enclosed attachment, which provides detailed written responses to the questions raised in your letter, informative. In addition to information regarding the supply, scheduling, and surveillance of marijuana, the response includes a detailed listing of the strains available through NIDA's contract with the University of Mississippi, and a thorough, step-by-step explanation of the process for researchers seeking to conduct marijuana research.

As you know, senior officials and subject matter experts from the Department of Health and Human Services (HHS), the Drug Enforcement Administration (DEA), and the Office of National Drug Control Policy (ONDCP) provided an in-person briefing for your staff on November 13, 2015, during which they shared a comprehensive overview of ongoing work to facilitate scientific research on the potential health benefits of marijuana, its components, and derivatives.

During this briefing, staff explained the specific roles of each agency as they relate to enforcement, regulatory, and research activity; identified the collaboration taking place at the federal level; discussed the requirements and limitations of the Single Convention on Narcotic Drugs, 1961 (Single Convention or "the treaty"); explained the specific requirements of the Controlled Substances Act (CSA) as they relate to scheduling and rescheduling; outlined the current federal portfolio regarding marijuana research; and walked through the process in which researchers ultimately can apply for and receive marijuana for research purposes.

Our agencies are committed to working together, along with federal, state, and local entities, to facilitate research and development efforts in accordance with the law. We support research on marijuana and its components that complies with applicable laws and regulations to advance our understanding about the health risks and potential therapeutic benefits of medications using marijuana or its components or derivatives. We will also provide this response to the co-signers of your letter.

Sincerely,

Sylvia M. Burwell, Secretary
U.S. Department of Health and Human Services

Michael Botticelli, Director
Office of National Drug Control Policy

Chuck Rosenberg, Acting Administrator
Drug Enforcement Administration

Attachment: Responses to Questions concerning Medical Marijuana Research

1. *The supply of marijuana for research purposes. DEA is charged with issuing permits for the bulk manufacture of marijuana for research purposes. The National Institute on Drug Abuse (NIDA) has an exclusive contract with the University of Mississippi (which holds the only bulk manufacture permit granted by DEA) to grow its entire research supply of marijuana. In our July 2015 letter, we raised concerns that this NIDA-held monopoly on supply of marijuana for research purposes limits access to adequate supply and appropriate varieties of marijuana and presents significant barriers to research.*

   At the November briefing, ONDCP and DEA indicated that they did not view supply limits as a barrier, citing a recent overproduction of one variety of marijuana for research and noting that DEA has only received one request for an additional bulk manufacture permit to date. But DEA assertions only applied to one strain of marijuana and do not reflect feedback we have heard from researchers in our states. Because the format of the briefing did not allow for discussion of this issue in appropriate detail, we therefore seek the following additional information:

a. Please provide detailed information on the current supply of marijuana at the University of Mississippi, including a breakdown of all strains, amounts available in each strain, amount of each strain that has been requested, and the amount of each strain that is in surplus.

As an entity registered under the CSA to manufacture marijuana, the University of Mississippi is responsible for maintaining records, including inventories of all stocks of controlled substances on hand.

Also under the CSA, DEA is responsible for issuing yearly aggregate production quotas (APQ) for each schedule I and II controlled substance. As part of this responsibility, DEA sets the individual manufacturing quota for marijuana produced by the University of Mississippi at the level sufficient to meet the estimated research needs of the United States. In establishing this production quota, DEA works closely with NIDA. Where NIDA indicates to DEA that there is a research need in the United States for a particular strain of marijuana, or for certain extracts thereof, DEA adjusts the APQ accordingly to ensure an adequate supply. In addition, consistent with the CSA and DEA regulations, registered manufacturers routinely provide DEA with information describing the desired manufacturing quota. These manufacturers may also contact DEA at any time throughout the year to request revisions to their quota. Regarding the surplus, DEA regulations provide that the quotas shall be sufficient to allow bulk manufacturers to maintain an inventory equal to 50 percent of its average estimated net disposal for the current calendar year.

The University of Mississippi currently has approximately 185 batches of marijuana with varying concentrations of tetrahydrocannabinol (THC) and cannabidiol (CBD) (**see Appendix A**). Many of these batches/strains have similar concentrations of THC and CBD and may be blended to achieve specific cannabinoid concentrations of interest to researchers. Bulk marijuana is generally available in the following 12 categories:

- Placebo marijuana (produced by solvent extraction)
  - THC (0%) / CBD (0%)
- Low THC varieties
  - Low THC (<1%) / Medium CBD (1-5%)
  - Low THC (<1%) / High CBD (5-10%)
  - Low THC (<1%) / Very High CBD (>10%)
- Medium THC varieties
  - Medium THC (1-5%) / Low CBD (<1%)
  - Medium THC (1-5%) / Medium CBD (1-5%)
  - Medium THC (1-5%) / High CBD (5-10%)
  - Medium THC (1-5%) / Very High CBD (>10%)
- High THC varieties
  - High THC (5-10%) / Low CBD (<1%)
  - High THC (5-10%) / High CBD (5-10%)
  - High THC (5-10%) / Very High CBD (>10%)
- Very high THC varieties
  - Very High THC (>10%) / Low CBD (<1%)

In addition, marijuana cigarettes are available with the following characteristics:

Batch #	**Marijuana Cigarettes**	**THC%**	**CBD%**	**cigarettes available**
11554-1005-62	Hand Rolled Placebo Marijuana Cigarettes, 70mm; 0.000%	0.00	No Data	14
12792-1208-77	Marijuana Cigarettes, 2.0% THC, 0.01% CBD	2.00	0.01	36000
12792-1208-77-Open	Marijuana Cigarettes, 2.0% THC, 0.01% CBD	2.00	0.01	119
10074-0301-97	Marijuana Cigarettes, 3.0% THC, 0.10% CBD	3.00	0.1	300
10074-0301-97-OP	Marijuana Cigarettes, 3.0% THC, 0.10% CBD	3.00	0.1	25
6567-0194-47	Marijuana Cigarettes, 3.2% THC, 0.12% CBD	3.20	0.12	300
12792-0109-120	Marijuana Cigarettes, 4.0% THC, 0.01% CBD	4.00	0.01	20400
12792-0109-120-Open	Marijuana Cigarettes, 4.0% THC, 0.01% CBD	4.00	0.01	114
12792-0109-146	Marijuana Cigarettes, 5.7% THC, 0.01% CBD	5.70	0.01	17400
12792-0109-146-Open	Marijuana Cigarettes, 5.7% THC, 0.01% CBD	5.70	0.01	428
10604-0203-95	Marijuana Cigarettes, High Potency, 7.4% THC, 0.22% CBD	7.40	0.22	56400
10604-0203-95-	Marijuana Cigarettes, High Potency;	7.40	0.22	305

OP	7.4% THC, 0.22% CBD			
12944-0509-105-Open	Placebo Marijuana Cigarettes, 0.004% THC, CBD not detected	0.00	No Data	122
12944-0509-105	Placebo Marijuana Cigarettes, 0.004% THC, CBD not detected	0.00	No Data	31200

In 2015, NIDA fulfilled 23 requests for marijuana from researchers (detailed in **Appendix B**). There are four additional requests currently pending as of February 5, 2016.

b. Please describe how agencies, including HHS, DEA, Department of Justice (DOJ), National Institutes of Health (NIH), NIDA, and the ONDCP, plan to increase the number of permits for the bulk manufacture of marijuana for research purposes. If there is no plan, please describe why not.

In determining how many persons may become registered as bulk manufacturers of marijuana for research purposes, DEA must adhere to the CSA and Single Convention. Under the CSA, DEA must limit the number of bulk manufacturers of marijuana "to a number of establishments which can produce an adequate and uninterrupted supply of [marijuana] substances under adequately competitive conditions for legitimate medical, scientific, research, and industrial purposes," 21 U.S.C. §823(a)(1). Under the Single Convention, DEA must ensure that registered manufacturers adhere to the system of controls required by the treaty, under which the United States Government must, among other things, maintain a monopoly on the distribution of cannabis material for research. The United States has historically met this treaty obligation through an arrangement whereby NIDA oversees the domestic production and distribution of marijuana by its contractor, the University of Mississippi.

As discussed during the briefing for your staff on November 13, 2015, the United States may, consistent with the CSA and Single Convention, expand the number of registered bulk manufacturers of marijuana, provided the statutory and treaty requirements are met. Among these requirements would be a determination by DEA (in consultation with NIDA) that the current NIDA contractor (the University of Mississippi) is unable to meet the demands of lawful researchers in the United States. While we cannot forecast the future interests of researchers, if such researchers required additional strains of marijuana that the University of Mississippi is unable to supply, this could provide a basis for DEA to register additional growers. Under such circumstances, for the United States to continue to meet its treaty requirements, any additional growers would likewise have to be acting under the direct control of the United States Government with respect to the production and distribution of the cannabis material.

c. Please indicate how many applications have been received for permits for bulk manufacture of marijuana for research purposes to date, what their status is, and the length of time between initial application and denial.

Since the enactment of the CSA in 1970, the only application by a person seeking to become registered as a bulk manufacturer of marijuana to supply researchers (in addition to the University of Mississippi) is that submitted by Lyle Craker, a researcher at the University of Massachusetts. An extensive analysis of that application and DEA's grounds for denial were

published in two documents in the Federal Register: 76 FR 51403 (2011) and 74 FR 2101 (2009). The decision by the DEA to deny the application was upheld by the United States Court of Appeals for the First Circuit in *Craker v. DEA*, 714 F.3d 17 (1st Cir. 2013).

d. Your response to our July letter indicates that DEA has approved 265 researchers to conduct medical marijuana research. For each of these approvals, please provide information on the requested strain, and how long it has taken to fulfill the researchers request for marijuana after the study has been approved.

Please note that the 265 researchers that DEA mentioned in the July letter were the number of persons registered with DEA to conduct research (clinical, preclinical, or analytical) with marijuana (including its constituents). A researcher who submits an application for such registration is not required to identify the strain of marijuana to be used in the research and DEA does not tabulate such data with respect to researchers.

Information on the marijuana NIDA sent to researchers in 2015 is included in Appendix B. On average, in 2015 shipments were sent about 25 days after the order was received. Shipments included:

- In 2010: 19 shipments to 9 researchers
- In 2011: 21 shipments to 8 researchers
- In 2012: 16 shipments to 9 researchers
- In 2013: 15 shipments to 8 researchers
- In 2014: 23 shipments to 12 researchers
- In 2015: 20 shipments to 8 researchers

To expedite fulfillment requests, all researchers are encouraged to contact NIDA during the registration process to ensure that their strains of interest are available or can be produced in sufficient quantities.

e. How are your agencies planning to work within the bounds of the Single Convention on Narcotics Drugs to allow researchers to utilize the already existing supply of marijuana in states that have enacted laws to make the drug available for medical or recreational use?

Please see the answer to question 1(b) and note that, under the Single Convention, the United States may not permit the production, distribution, or use of marijuana produced outside the system of controls described under the treaty.

f. The United Kingdom, Canada, Israel, the Netherlands, Czech Republic, Portugal, and Uruguay have acted to increase the diversity of sources for the production of marijuana for research while still complying with the Single Convention on Narcotic Drugs. Why has the United States not taken similar actions?

The International Narcotics Control Board is the component of the United Nations responsible for monitoring compliance with the treaties. Please see the answer to question 1(b) for an explanation of how the registration of additional marijuana growers to supply

researchers in the United States might be carried out in conformity with the CSA and the Single Convention. We do not have sufficient information regarding the cultivation of cannabis in these other nations on which to base an opinion as to whether such activity is in compliance with international treaty obligations.

2. Assessment of marijuana rescheduling. In our July letter, we asked about the timeline for the Food and Drug Administration (FDA) to complete its analysis on the rescheduling of marijuana and to make a recommendation to DEA. We also asked what the DEA timeline was for assessment upon receipt of FDA recommendation. These questions were not answered in the written response from your agencies, and at the staff briefing you repeatedly informed our staff that you could not provide the requested information. However, after the briefing we learned that in fact FDA has already made the recommendation. In a September 30, 2015, letter to Congressman Earl Blumenauer, DOJ wrote that "DEA recently received the HHS scientific and medical evaluations as well as a scheduling recommendation," which indicates FDA has completed its evaluation, and that "DEA is currently reviewing these documents ... to make a scheduling determination in accordance with the Controlled Substances Act." Failure to provide us with this information at the briefing leaves us with continued questions about the process and timeline for a re-scheduling determination. We therefore ask that you provide us with the following information:

a. Please confirm whether or not DEA has received the HHS evaluations and scheduling recommendations.

DEA has received the HHS scientific and medical evaluations, as well as a scheduling recommendation, and is currently reviewing these documents and all other relevant data to make a scheduling determination in accordance with the CSA.

b. What is the DEA timeline for assessment upon receipt of the FDA recommendation?

DEA will carry out its assessment of the FDA recommendation in accordance with the CSA requirements set forth in 21 U.S.C. §§ 811 and 812. Once a final determination has been made, DEA will notify the petitioners. DEA understands the widespread interest in the prompt resolution of these petitions and hopes to release its determination in the first half of 2016. Our staff would be happy to share the final assessment with your offices when available.

c. Has DEA requested that FDA complete a scientific analysis for the rescheduling of cannabadiol (CBD)? If so, please describe how FDA will conduct the review.

DEA, FDA, and NIDA have been working together to address the issues relating to CBD, including scheduling considerations. The scheduling determinations must undergo a scientific and deliberate interagency process (see **Appendix C**). NIDA and FDA have been working to complete an extensive literature review of human and animal studies that have evaluated CBD in terms of its abuse potential, pharmacology chemistry, adverse effects and dependence. However, FDA has indicated that a human abuse liability study may be necessary to make a final determination on abuse potential. FDA and NIDA have been exploring options for completing this study to generate this data. In carrying out scheduling activities related to CBD, DEA and

FDA will follow the procedures set forth in 21 U.S.C. § 811 and § 812.

3. Interagency coordination and research applications. At the briefing, you explained to us that ONDCP is coordinating regular meetings with relevant federal agencies about encouraging research, and you explained that these discussions ultimately led to the elimination of the HHS Public Health Service Review Board. This was a positive step, because this board significantly delayed research approval and existed for no other Schedule I substance. However, we continue to hear from the research community that the research application approval process is long, cumbersome, and difficult to navigate. We therefore ask that you:

a. Please clarify how you plan to work together to encourage qualified research applications.

We recognize that the current process for initiating research on marijuana or its constituent compounds is time consuming and some researchers have indicated to NIDA that this can be a disincentive to conducting research in this area. HHS and DEA have been working together to explore ways to streamline the process by which marijuana-related research may be conducted while also meeting our international and legislative obligations under the Single Convention and the CSA to control the production and distribution of marijuana for research purposes to prevent diversion.

In addition to eliminating the Public Health Service (PHS) committee review for non-federally funded marijuana research (discussed in our last letter), DEA recently streamlined the administrative process for CBD research. In the past, researchers who expanded the scope of their approved studies and needed more CBD than initially anticipated had to request, in writing, a modification to their DEA research registrations—potentially delaying that research while the modification underwent an approval process that included both DEA and FDA. The new policy removes this step for previously registered CBD clinical researchers who are granted a waiver. [1]

Steps like these represent our commitment to work together to identify ways of streamlining research on marijuana and its constituents.

DEA and NIDA continue to meet to explore other potential steps that can be taken to facilitate research with marijuana and its constituents.

b. Please describe the application process for qualified researchers who wish to conduct research using marijuana, including all steps at DEA, FDA, and local Institutional Review Boards, from initial application to receipt of marijuana from NIDA, including data on how long the entire process has taken for previously approved applications.

The application process for persons seeking to become registered to conduct research with marijuana (or any other schedule I controlled substance) is set forth in 21 U.S.C. § 823(f) and 21 CFR 1301.18 and 1301.32. We note that in addition to the process outlined below, applicants

[1] http://www.dea.gov/divisions/hq/2015/hq122315.shtml

must adhere to particular state, local, and/or institutional requirements.

The process for conducting research using marijuana or components of marijuana includes:

1. A review of scientific validity and ethical soundness.

    a. For NIH-funded research, this occurs through the NIH grant review process and consists of three steps that take approximately nine months (which is the same amount of time taken to review grants for non-marijuana related research):
        i. The NIH peer review system, which assesses the scientific and technical merit of all grant applications;
        ii. Review by the National Advisory Council of the funding Institute, comprising eminent scientists as well as public members; and
        iii. Review by the Director of the funding Institute, who makes the final decision on the merit of an application for funding, based on peer review, public health significance, and Institute priorities.

    [Note: review by the institutional review board (IRB) of the researchers organization occurs before NIH review]

    b. For non-NIH funded basic research, not involving human subjects, the research protocol is reviewed for scientific merit by a minimum of two non-government scientists, identified by the NIDA Drug Supply Program, with expertise in the research topic. This step typically takes 4-6 weeks but can take longer if the reviewers have additional questions or concerns that need to be addressed by the researcher. As with all requests for controlled substances from NIDA's Drug Supply Program, investigators must submit a detailed research protocol including:
        i. The specific aims and goals of proposed study;
        ii. The experimental design, including the number of experiments and experimental subjects and the dosages or concentration of drugs;
        iii. Justification of quantities of drug(s) requested; and
        iv. A document demonstrating that the research is approved by the Animal Care & Use Committee and that adequate care in conducting animal research will be exercised (if applicable).
        v. Documentation of local IRB approval.

2. For research involving human subjects (whether NIH-supported or not), the researcher must also have an active-status Investigational New Drug (IND) application on file with FDA, which has been evaluated by FDA and found safe to proceed. FDA reviews scientific validity and ethical soundness. The review assures the safety and rights of subjects and the scientific quality of the clinical investigations, and assesses the likelihood that investigations will yield data capable of meeting the statutory standards for drug marketing approval. FDA has a 30-day regulatory timeframe for completion of this review. The researcher may start the study(ies) after 30 days, unless notified by FDA that the study(ies) are on hold (may not proceed until certain deficiencies are resolved) or on notification by FDA that the study(ies) may start sooner.

3. For all research (involving animal or human subjects), the researcher must obtain a DEA registration for marijuana, a Schedule I controlled substance. However, it should be noted that some states have separate registration requirements that often need to be completed sequentially. [2], [3] Obtaining a DEA registration includes:
    a. Completing and submitting a DEA application for each Schedule I drug used:
        i. The applicable fee is currently $244 for a one-year registration period.
        ii. The application includes the research protocol and the amount of drug needed for the study.

    b. A DEA investigator conducts a site visit to ensure that diversion controls are in place.

    c. DEA sends the research protocol to FDA for review. Once received, FDA has 30 days to review and respond to DEA about protocols involving human subjects and 21 days to respond for protocols involving non-human research. However, if more information is needed from the researcher, the DEA investigator will contact the researcher which can extend the time.

    d. Once all of the DEA requirements have been satisfied, the researcher will receive a DEA registration number. This typically occurs within an average of 62 days after receiving input from FDA.
        i. Registration needs to be renewed every year.

    e. A local IRB approval must accompany the application for registration (DEA Form 225).

4. When the above steps have been completed, investigators contact the NIDA Drug Supply Program to place an order for marijuana with specific characteristics regarding concentrations of THC, CBD, and other cannabinoids. The program official verifies that the application is complete (with all the above-mentioned steps fulfilled), and forwards the order to the contractor responsible for shipping the marijuana. This process typically takes about two to four weeks.
    a. Researchers are encouraged to contact NIDA before all of the above steps have been completed to ensure that their strains of interest are already available or can be produced in sufficient quantities.

    Please note that the majority of the applications that DEA receives do not conform to the application requirements. In these instances, DEA works with the applicant to obtain the information missing before initiating the interagency review process described above.

4. Surveillance and epidemiological studies. Federal agencies should work to facilitate surveillance and epidemiological studies to assess how medical marijuana is being used. This should also include investigations in diverse populations and with multiple modes of

[2] https://www.txdps.state.tx.us/internetforms/Forms/NAR-77-78.pdf
[3] http://www.ct.gov/DCP/cwp/view.asp?a=1622&Q=500858&PM=1

administration. We inquired about this work in our initial letter and our briefing, and we are concerned that there was no mention of efforts to collect these data. We therefore ask that you address the following:

a. Is the Centers for Disease Control and Prevention (CDC), in collaboration with NIDA and any other federal agencies, collecting data about the total number of medical marijuana patients in the United States, the nature of their ailments, modes of use, and patient reported outcomes?

We note that the Substance Abuse and Mental Health Services Administration (SAMHSA), CDC, and NIH will continue to conduct routine monitoring of marijuana use through the National Survey on Drug Use and Health, the Youth Risk Behavior Surveillance System, and the Monitoring the Future survey, respectively. Currently, these surveys do not collect information that distinguishes medical use from recreational use.

Additionally, CDC is in the process of modifying questions asked on the annual Behavioral Risk Factor Surveillance Survey (BRFSS) to better understand patterns of use of marijuana broadly. These questions may be added either as an optional module which states decide whether or not to administer, or as part of the core survey set. These added questions will increase our understanding of patterns of marijuana use -- in terms of frequency, mode of use, and self-report regarding whether use was for medical, recreational, or both purposes.

At the population level, drawing a line between medical and recreational use is challenging for multiple reasons. For example, a previous study conducted by CDC utilizing an online survey called Healthstyles examined self-reported reasons for using marijuana, and among current users found that 53 percent reported using for recreational reasons only, 10 percent medical only, and 36 percent reported using for both recreational and medical reasons. Of all those reporting use for medical purposes, more than three quarters also used marijuana recreationally.[4]

There is also broad variation from state-to-state around reporting requirements, including some states that have no reporting or state-level registry and thus cannot address the questions raised such as total number of medical marijuana users, nature of ailments addressed, modes of use, and patient outcomes. To our knowledge, even in states with patient-level registries, mode of use and patient reported outcomes are not collected.

We anticipate future work with federal agencies and states to attempt to increase the collection of usable data, both from enhanced federal and state surveys of the general population, as well as from medical marijuana registries where these exist and from chronic disease registries.

b. How are your agencies working with state public health departments in order to coordinate research on medical marijuana use so that data can be compared between states?

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[4] Schauer G et al, Toking, Vaping and Eating for Health or Fun: Marijuana Use Patterns in Adults, U.S., 2014. American Journal of Preventive Medicine 2015

CDC helped facilitate communication between the four states that have legalized recreational use, including coordination of public health surveillance and research efforts. However, as noted above, these states have not drawn strict demarcation lines between data collection on public health issues associated with medical and recreational use.

In addition, CDC and SAMSHA are currently working with states through an effort coordinated by the Council of State and Territorial Epidemiologists to develop uniform surveillance questions, including a question to address medical use, that can be integrated into state and national surveillance systems and facilitate state-to-state comparisons. A similar process was used to develop a marijuana surveillance module for the 2016 BRFSS (mentioned above) and is expected to guide the development of modules for other CDC public health surveillance systems that collect state-specific, population-based data, like the Pregnancy Risk Assessment Monitoring System (PRAMS).

c. *How are your agencies ensuring that studies on the benefits of medical marijuana include diverse populations?*

Applications for NIH funding are required to detail plans for the inclusion of women, minorities, and children. Specifically, when the proposed project involves human subjects, the review committee evaluates the proposed plans for the inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (or exclusion) of children to determine if it is justified in terms of the scientific goals and research strategy proposed. Additional information on this review is included in the Guidelines for the Review of Inclusion in Clinical Research (**see Appendix D**).

d. Please describe in detail what measures are being taken to encourage research that investigates the variable risks, benefits, and efficacy of different modes of administration, including smoking, inhalation of vaporized product, oral administration of cannabis, and types of products, including purified products or specific compounds?

NIH supports and conducts a broad portfolio of research regarding the potential therapeutic benefits and harms of marijuana and its constituent components. NIH supports a diverse portfolio of research on cannabinoid compounds that in fiscal year (FY) 2015 spanned more than half of the NIH Institutes and Centers and totaled more than $110 million. Examples of funded studies include:

- The basic biology of the endocannabinoid system
  1. Pharmacological activity of cannabinoids and cannabinoid receptors
  2. Endocannabinoid signaling during pregnancy
  3. Genetic and environmental impact on risk for marijuana use
- Therapeutic effects of cannabinoids
  1. The efficacy of CBD and THC for treatment of pain
  2. Cannabinoids including CBD and nabilone as treatments for substance use disorders (opioids, alcohol, cannabis, and methamphetamine)
  3. The use of cannabinoids to treat cannabis use disorder
  4. The impact of the endogenous cannabinoid system on pain, traumatic brain injury,

and substance use disorders

- Risks associated with marijuana use
  1. Effects of smoked cannabis on driving
  2. Immunosuppression associated with CBD
  3. Epigenetic, neurological, psychiatric, and cognitive effects of heavy cannabis use
- Routes of administration
  1. Transdermal delivery of CBD to treat alcoholism
  2. Acute and chronic effects of vapor inhalation of synthetic cannabinoids
  3. Development of a standard vaporizer system for use in research
  4. Development of a rodent self-administration system for vapor inhalation of THC for pre-clinical studies
- The impact of changing state policies on use of marijuana and related health and other outcomes

In addition, to support additional research in this area NIH has issued funding opportunity announcements that focus on:

1. Developing the Therapeutic Potential of the Endocannabinoid System for Pain Treatment[5]
2. Effects of Cannabis Use and Cannabinoids on the Developing Brain[6]
3. Clinical Evaluation of Adjuncts to Opioid Therapies for the Treatment of Chronic Pain (including cannabinoids)[7]

In March 2016, NIH will hold a neuroscience research summit on Marijuana and Cannabinoids[8] to discuss the state of science on marijuana's harms as well as its potential therapeutic uses, focusing on neurologic and psychiatric disorders. The meeting is being sponsored by several NIH Institutes and Centers: NIDA; the National Institute on Alcohol Abuse and Alcoholism; the National Center for Complementary and Integrative Health, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke.

e. Canada and the state of California have established medical marijuana patient registries. A patient registry could significantly support the work of researchers and physicians, while also improving our understanding of the population of medical marijuana patients in the United States. We understand that NIDA is analyzing these programs to determine the feasibility of a national patient registry. Please describe any ongoing work to establish a national patient registry, including any necessary funding that would be necessary to launch this effort, and the timeline for implementation.

We are aware of the registry being developed in Canada to collect health outcome and safety information on medical marijuana patients; however, to our knowledge the State of California has not yet set up a similar registry. Marijuana use registries could provide a resource to help target research, and NIDA has been exploring the possibility of funding researchers to analyze

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[5] PA-15-188
[6] PA-14-163
[7] PAR-14-225
[8] http://apps1.seiservices.com/nih/mj/2016/Default.aspx

data from existing registries. Given the disparities between federal and state laws on use or marijuana for medical conditions, we are not considering a national registry.

5. Coordination with states and inter-agency cooperation. Cooperation is vital to ensure that medical marijuana is being used effectively and appropriately by those who need it. We asked a number of questions about such cooperation in our letter and our briefing and the responses were not complete. For example, you informed us that federal agencies have been in communication and are coordinating on this issue, but failed to describe in detail the nature and type of these communications. We therefore ask that you address the following:

a. Please describe in detail any regular and organized communication between HHS and state public health departments to coordinate research efforts regarding medical marijuana.

FDA encourages and supports medical research into the safety and efficacy of marijuana products through adequate and well-controlled clinical trials conducted under an IND and consistent with DEA requirements for research on Schedule I substances. FDA has talked with representatives from several states as they consider support for medical research of marijuana and its derivatives to provide scientific advice and to help ensure that their research is rigorous and appropriate.

FDA has also been in communication with individual states to exchange information on the number and types of reported adverse events related to the use of products containing marijuana and marijuana-derivatives which are currently being marketed, and has provided technical support to states that have made marijuana available under state law and are interested in supporting the conduct of medical research to be carried out in conformity with federal law.

b. Please describe in detail any efforts by federal agencies to provide guidance to states for testing standards to ensure patient safety and access needs are met.

Please see the answer to 5(a) above.

c. Please describe in detail any regular and organized communication taking place between agencies that are charged with marijuana research, policy, or data collection (including but not limited to CDC, FDA, NIH, ONDCP, and SAMHSA), to coordinate efforts and long term plan development.

The HHS Secretary's Behavioral Health Coordinating Council (BHCC) is a coordinating body within the Department, established in 2010, to share information and identify and facilitate collaborative, action-oriented approaches to address the HHS behavioral health agenda without duplicating efforts. A BHCC Marijuana Subcommittee was established a few years ago and focuses on four key areas of HHS engagement—research and surveillance; regulatory oversight; education; and treatment. This group is in regular communication and meets as needed to address concerns.

Further, ONDCP has been convening regular meetings and calls for relevant federal agencies, such as HHS, NIDA, FDA, CDC, SAMHSA, DEA, and DOJ, to exchange

information on marijuana-related activities and to discuss opportunities for collaboration on issues related research, policy, or data collection.

ONDCP has also convened more targeted meetings of specific federal agencies to discuss how to stimulate research on marijuana, including the potential therapeutic benefits of marijuana and its constituent components.

Appendix A: NIDA Stocks of Marijuana as of January 6, 2016**

Batch No.	Description	THC (%)	CBD (%)	2015 Inventory Weight (kilograms)
	High THC /Low CBD			
1304-1	HIGH POTENCY (Reprocessed)	13.17	0.05	0.37
1290A	HIGH CBD/HIGH THC (Reprocessed)	9.85	0.02	0.32
1426	MX	9.54	0.00	8.83
1357	High THC Clones (MX)	8.74	0.11	2.74
1431	MX	8.48	0.14	1.42
1291C	HIGH CBG/HIGH THC (Reprocessed)	8.45	0.04	0.37
1292A	HIGH CBG/HIGH THC	8.44	0.03	0.15
1292	HIGH THC	8.38	0.00	0.26
1313	HIGH POTENCY	8.29	0.00	8.12
1324	High THC Clones (MX)	7.96	0.02	14.75
1424	MX	7.26	0.32	3.18
1309	HIGH POTENCY	7.07	0.00	16.78
1428	MX	7.06	0.00	7.51
1427	MX	6.97	0.00	3.82
1291	HIGH THC	6.95	0.06	0.56
1296	HIGH POTENCY	6.94	0.00	14.43
1308	HIGH POTENCY	6.68	0.00	4.57
1430	MX	6.67	0.00	8.30
1306	HIGH POTENCY	6.27	0.00	5.40
1289A	HIGH CBG/HIGH THC	6.11	0.04	0.25
1300	HIGH POTENCY	6.01	0.00	15.80
1297	HIGH POTENCY	5.83	0.00	13.88
1299	HIGH POTENCY	5.78	0.00	13.70
1272	HIGH POTENCY	5.64	0.00	4.57
1314	HIGH POTENCY	5.62	0.00	7.85
1291D	HIGH THC/CBD~CBN	5.58	0.31	0.08
1315	HIGH POTENCY	5.34	0.00	10.38
1425	MX	5.30	0.16	1.50
1273	HIGH POTENCY	4.96	0.00	6.71
1432	MX	4.96	0.00	0.32
1429	MX	4.93	0.00	1.12
1298	HIGH POTENCY	4.89	0.00	16.08
1379	High THC/Low CBD MX Clones (Mixed	4.83	0.17	1.71

	Fines)			
1289	HIGH THC	4.75	0.00	0.54
1290C	MED CBD/LOW THC	4.39	1.09	0.09
1290	HIGH THC	4.24	0.66	0.74
1302	HIGH POTENCY	2.78	0.03	11.06
1305	HIGH POTENCY	2.66	0.00	7.01
1303	HIGH POTENCY	2.44	0.00	10.72
1307	HIGH POTENCY	2.22	0.00	12.38
1200	CMEF-00	1.65	0.00	2.84
1200		1.29	0.00	0.93
1158	CMEF-01	1.43	0.00	9.86
1317	HIGH THC CLONES-NonGMP	8.78	0.01	4.78
	Low THC / High CBD			
1375B	Fines (Mixed Fines) [Reprocessed}	1.26	23.91	0.03
1371A	Fines (V1-20) {Reprocessed}	0.96	21.46	0.06
1375A	High CBD/Low THC Clones (Mixed Fines) {Reprocessed}	0.52	13.96	0.04
1371	Low THC/High CBD Clones (V1-20) {Reprocessed}	0.42	11.13	3.77
1368	Low THC/High CBD Clones (V1-30)	0.43	9.62	1.83
1345	Low THC/High CBD Clones (V1-20)	0.21	6.49	12.22
1348	Low THC/High CBD Clones (V1-20)	0.22	6.47	12.85
1341	Low THC/High CBD Clones (V1-20)	0.23	6.47	12.06
1333	Low THC/High CBD Clones (V1-30)	0.24	6.45	10.79
1381	V1-16	0.39	6.12	1.69
1328	Low THC/High CBD Clones (V1-20)	0.27	6.10	7.22
1334	Low THC/High CBD Clones (V1-30)	0.22	6.08	9.97
1340	Low THC/High CBD Clones (V1-20)	0.21	5.99	12.61
1329	Low THC/High CBD Clones (V1-20)	0.25	5.99	10.66
1346	Low THC/High CBD Clones (V1-20)	0.19	5.96	12.35
1339	Low THC/High CBD Clones (V1-20)	0.21	5.92	13.04
1332	Low THC/High CBD Clones (V1-30)	0.24	5.86	11.46
1350	Low THC/High CBD Clones (V1-20)	0.22	5.72	11.07
1383	V1-20	0.22	5.68	3.55
1349	Low THC/High CBD Clones (V1-20)	0.19	5.67	11.88
1353	Low THC/High CBD Clones (V1-30)	0.22	5.66	13.49
1342	Low THC/High CBD Clones (V1-20)	0.20	5.66	13.12
1351	Low THC/High CBD Clones (V1-30)	0.18	5.65	11.83
1331	Low THC/High CBD Clones (V1-30)	0.23	5.63	4.55
1347	Low THC/High CBD Clones (V1-20)	0.18	5.61	11.83

1386	V1-20	0.18	5.56	4.20
1337	Low THC/High CBD Clones (V1-30)	0.19	5.55	11.10
1343	Low THC/High CBD Clones (V1-20)	0.18	5.55	12.26
1389	V1-20	0.20	5.55	3.11
1344	Low THC/High CBD Clones (V1-20)	0.20	5.51	14.32
1336	Low THC/High CBD Clones (V1-16)	0.29	5.39	10.90
1338	Low THC/High CBD Clones (V1-20)	0.18	5.38	0.00
1387	V1-20	0.18	5.34	3.63
1335	Low THC/High CBD Clones (V1-19)	0.23	5.28	0.00
1356	Low THC/High CBD Clones (V1-30)	0.21	5.26	6.90
1403	B4	0.32	4.97	2.99
1352	Low THC/High CBD Clones (V1-30)	0.16	4.95	6.43
1384	V1-20	0.18	4.94	2.14
1398	V1-30	0.17	4.90	6.87
1385	V1-20	0.16	4.82	4.19
1370	Low THC/High CBD Clones (V1-20)	0.19	4.73	11.32
1390	V1-20	0.15	4.68	5.06
1388	V1-20	0.14	4.61	4.80
1392	V1-20	0.14	4.52	4.51
1369	Low THC/High CBD Clones (V1-30)	0.18	4.50	0.00
1391	V1-20	0.18	4.42	4.45
1393	V1-19	0.21	4.36	1.65
1399	V1-30	0.13	4.16	5.39
1395	V1-30	0.15	4.15	0.23
1330	Low THC/High CBD Clones (V1-20)	0.15	3.88	10.34
1417	V6-8	0.16	3.36	0.75
1380	V 1 Leaves	0.13	3.80	3.80
1396	V1-14	0.15	3.75	1.30
1394	V1-30	0.12	3.55	0.69
1416	V6-8	0.16	3.30	0.07
1397	V1-14	0.25	3.23	9.23
1382	V1-16	0.14	3.12	1.63
1418	B5	1.03	2.89	1.42
	Mixed Varieties			
1423	MX-Leaves	7.47	3.31	12.68
1322	Medium THC/CBD Clones (A-17)	3.32	4.02	4.90
1323	Medium THC/CBD Clones (A-17)	3.49	4.17	4.52
1325	Medium THC/CBD Clones (B4)	3.88	5.38	12.74
1326	Medium THC/CBD Clones (B4)	4.25	6.03	13.20

1327	Medium THC/CBD Clones (B4)	5.16	6.80	8.41
1354	Medium THC/CBD Clones (B-5)	2.97	4.89	6.46
1355	Medium THC/CBD Clones (B-4)	3.91	5.99	12.25
1358	Medium THC/CBD Clones (B-4)	4.29	6.20	11.79
1359	Medium THC/CBD Clones (B-4)	4.78	6.85	10.95
1360	Medium THC/CBD Clones (B-4)	4.40	6.50	10.70
1361	Medium THC/CBD Clones (B-4)	3.97	5.82	11.88
1362	Medium THC/CBD Clones (B-4)	4.33	6.27	10.32
1363	Medium THC/CBD Clones (B-4)	4.71	6.70	16.81
1364	Medium THC/CBD Clones (B-4)	4.31	6.06	11.99
1365	Medium THC/CBD Clones (V3-22)	1.36	3.14	10.20
1366	Medium THC/CBD Clones (V3-22)	1.58	3.46	10.63
1367	Medium THC/CBD Clones (V6-8)	2.85	4.93	13.35
1372	Medium THC/CBD Clones (B-4)	3.54	5.41	5.11
1373	Medium THC/CBD Clones (V3-15)	2.29	4.05	11.50
1374	Medium THC/CBD Clones (V3-15)	3.17	5.03	11.71
1377	CBD/THC Clones (Mixed Fines)	1.81	3.38	8.78
1291A	THC~CBD	4.43	4.92	0.00
1376A	High CBD/Medium THC Clones (Mixed Fines) {Reprocessed}	3.05	13.66	1.70
1376B	Fines (Mixed Fines) [Reprocessed}	7.04	20.72	0.28
1378A	High CBD/High THC Clones (Mixed Fines) {Reprocessed}	9.13	15.49	0.11
1378B	Fines (Mixed Fines) {Reprocessed}	8.44	16.74	0.08
1406	B4	2.72	4.65	2.02
1415	V1-15	2.17	3.80	5.14
1400	B5-Leaves	2.66	4.39	6.82
1413	A18	3.28	4.38	0.86
1419	B6-8	3.98	5.27	1.60
1405	B4	2.82	4.38	2.76
1404	B4	3.51	4.79	4.70
1402	B4	2.85	4.91	6.39
1412	A18	3.98	5.27	1.05
1407	B4	3.91	5.82	6.76
1414	B5-Leaves	3.79	6.39	1.19
1408	B4	3.14	4.80	4.10
1409	B4	4.08	6.07	3.92
1410	B4	3.38	5.11	4.42
1401	B4	2.79	4.50	2.74
1420	B3-15			1.54

1421	B4	2.72	4.65	5.60
1411	A17	2.62	3.54	0.83
1422	V3-15	1.64	3.17	11.53
	Bulk Material			
	HIGH POTENCY MARIJUANA PLANT MATERIAL BULK	6.70		0.93
1200	MARIJUANA PLANT MATERIAL BULK	1.29		0.04
1231	MARIJUANA PLANT MATERIAL BULK	3.53		0.04
1232	MARIJUANA PLANT MATERIAL BULK	8.16		4.00
090709A	MARIJUANA PLANT MATERIAL BULK	6.44		0.25
1352	MARIJUANA PLANT MATERIAL BULK	0.10	4.10	4.99
1371	MARIJUANA PLANT MATERIAL BULK	0.42	11.13	1.99
1375A	MARIJUANA PLANT MATERIAL BULK	0.47	11.41	1.99
1024	MARIJUANA PLANT MATERIAL BULK	1.20	0.00	2.98
1200	MARIJUANA PLANT MATERIAL BULK	1.20	0.01	1.99
1304-1	MARIJUANA PLANT MATERIAL BULK	10.10	0.04	1.99
1304-1	MARIJUANA PLANT MATERIAL BULK	12.60	0.04	4.95
13494-22	MARIJUANA PLANT MATERIAL BULK	14.10	0.03	0.93
1009	MARIJUANA PLANT MATERIAL BULK	2.00	0.16	1.51
13322-21-1	MARIJUANA PLANT MATERIAL BULK	3.10	0.01	1.08
1327	MARIJUANA PLANT MATERIAL BULK	4.00	6.70	4.99
1291-A	MARIJUANA PLANT MATERIAL BULK	4.50		0.35
1291-A	MARIJUANA PLANT MATERIAL BULK	4.50	5.31	0.19
13322-21-2	MARIJUANA PLANT MATERIAL BULK	4.70	0.01	1.82
12792-143-7	MARIJUANA PLANT MATERIAL BULK	6.10	0.01	13.54
1292	MARIJUANA PLANT MATERIAL BULK	6.70	0.03	0.19
1378A	MARIJUANA PLANT MATERIAL BULK	7.50	13.80	2.93
13851-0715-139	MARIJUANA PLANT MATERIAL BULK	7.70	7.90	2.93
13494-8	MARIJUANA PLANT MATERIAL BULK	7.90	0.05	0.92
1266	MARIJUANA PLANT MATERIAL BULK	8.40	0.04	3.06
3857-105-10	MARIJUANA PLANT MATERIAL BULK	6.50	0.01	3.99
12792-1208-77A	MARIJUANA PLANT MATERIAL BULK	1.10	0.00	0.70
12792-0109-145-1	MARIJUANA PLANT MATERIAL BULK	5.50	0.02	12.99
	MARIJUANA PLANT MATERIAL BULK	2.22		10.00
	MARIJUANA PLANT MATERIAL BULK	2.41		0.13
	MARIJUANA PLANT MATERIAL BULK	4.06		0.13
	MARIJUANA PLANT MATERIAL BULK	8.04		0.13

12944-0509-105-1	PLACEBO MARIJUANA PLANT MATERIAL BULK	0.01	nd	2.70
13322-21-3	PLACEBO MARIJUANA PLANT MATERIAL BULK	0.02	nd	1.77
4022-0598-111-1	PLACEBO MARIJUANA PLANT MATERIAL BULK	0.01	nd	2.22
	PLACEBO MARIJUANA PLANT MATERIAL BULK			0.30
	MARIJUANA PLANT MATERIAL BULK			5.00
	Marijuana Cigarettes			**cigarettes**
11554-1005-62	Hand Rolled Placebo Marijuana Cigarettes, 70mm; 0.000%	0.00		14
12792-1208-77	Marijuana Cigarettes, 2.0% THC, 0.01% CBD	2.00	0.01	36000
12792-1208-77	Marijuana Cigarettes, 2.0% THC, 0.01% CBD	2.00	0.01	119
10074-0301-97	Marijuana Cigarettes, 3.0% THC, 0.10% CBD	3.00	0.1	300
10074-0301-97	Marijuana Cigarettes, 3.0% THC, 0.10% CBD	3.00	0.1	25
6567-0194-47	Marijuana Cigarettes, 3.2% THC, 0.12% CBD	3.20	0.12	300
12792-0109-120	Marijuana Cigarettes, 4.0% THC, 0.01% CBD	4.00	0.01	20400
12792-0109-120	Marijuana Cigarettes, 4.0% THC, 0.01% CBD	4.00	0.01	114
12792-0109-146	Marijuana Cigarettes, 5.7% THC, 0.01% CBD	5.70	0.01	17400
12792-0109-146	Marijuana Cigarettes, 5.7% THC, 0.01% CBD	5.70	0.01	428
10604-0203-95	Marijuana Cigarettes, High Potency, 7.4% THC, 0.22% CBD	7.40	0.22	56400
10604-0203-95	Marijuana Cigarettes, High Potency; 7.4% THC, 0.22% CBD	7.40	0.22	305
12944-0509-105	Placebo Marijuana Cigarettes, 0.004% THC, CBD not detected	0.00	nd	122
12944-0509-105	Placebo Marijuana Cigarettes, 0.004% THC, CBD not detected	0.00	nd	31200

***nd- not detected**

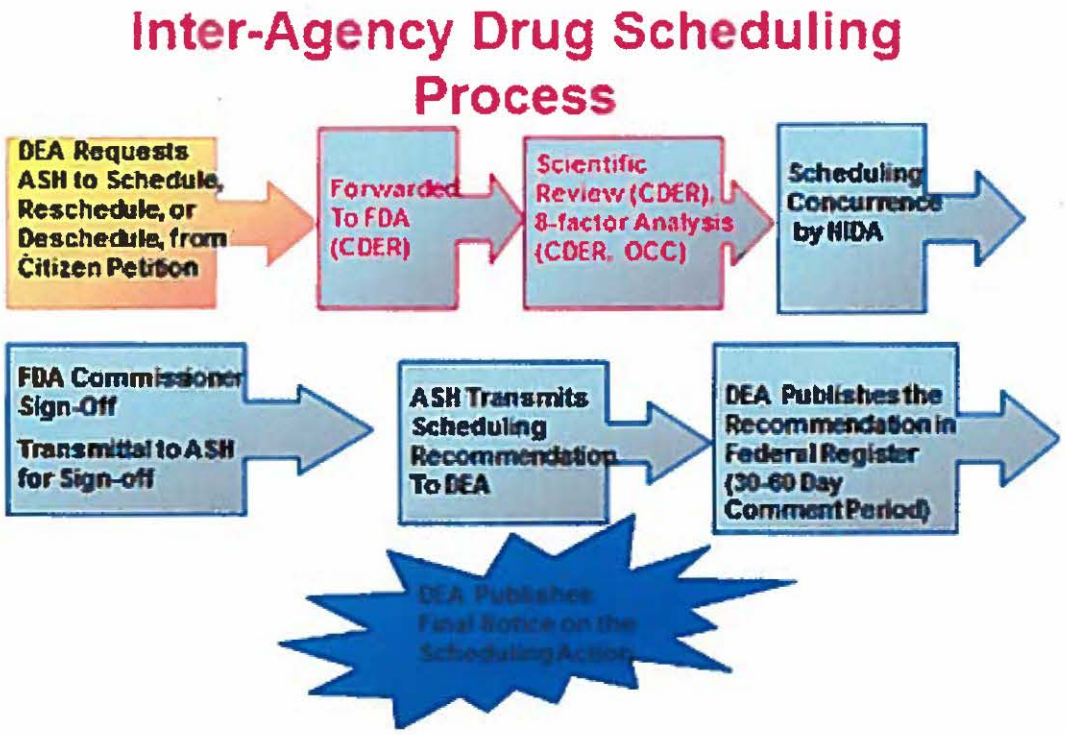
****please note descriptions in Appendix A are for internal cataloging purposes only.**

Appendix B: Shipments/ Pending Requests of Marijuana Cigarettes and Bulk Material – 2015 (Report as of January 6, 2015)

Ship Date	Compound	Shipped	Unit of Measure
3/30/2015	Marijuana Cigarettes, 5.7% THC, 0.01% CBD	300	cig
3/30/2015	Placebo Marijuana Cigarettes, 0.004% THC, CBD not detected	300	cig
4/20/2015	Marijuana Cigarettes, 5.7% THC, 0.01% CBD	300	cig
4/20/2015	Placebo Marijuana Cigarettes, 0.004% THC, CBD not detected	300	cig
5/20/2015	Marijuana Plant Material Bulk 14.1% THC, 0.03% CBD	0.001	grams
5/20/2015	Marijuana Plant Material Bulk 2.0% THC, 0.16% CBD (UMISS Batch # 1009)	0.99938	grams
5/20/2015	Marijuana Plant Material Bulk 4.7% THC, 0.01% CBD	0.99982	grams
5/20/2015	Marijuana Plant Material Bulk 7.9% THC, 0.05% CBD	1	gram
6/8/2015	Marijuana Cigarettes, 5.7% THC, 0.01% CBD	1800	cig
6/9/2015	Marijuana Cigarettes, 4.0% THC, 0.01% CBD	1800	cig
6/25/2015	Marijuana Plant Material Bulk 4.%THC, 6.7%CBD (Batch/Barrel#1327)	600	grams
6/30/2015	Marijuana Plant Material Bulk 1.2% THC, 0.00% CBD (UMISS Batch # 1024)	24.998	grams
7/23/2015	Marijuana Plant Material Bulk 1.2%THC, 0.01%CBD (Batch/Barrel#1200)	100	grams
7/23/2015	Marijuana Plant Material Bulk 4.5%THC, 5.31%CBD (Batch/Barrel#1291A)	100	grams
7/23/2015	Marijuana Plant Material Bulk 6.7%THC, 0.03%CBD (Batch/Barrel#1292)	99.999	grams
7/23/2015	Placebo Marijuana Plant Material Bulk 0.026% THC, CBD not detected	99.999	grams
11/9/2015	Marijuana Cigarettes, 4.0% THC, 0.01% CBD	1800	cig
11/17/2015	Marijuana Cigarettes, 4.0% THC, 0.01% CBD	36	cig
11/17/2015	Placebo Marijuana Cigarettes, 0.004% THC, CBD not detected	20	cig
12/2/2015	Marijuana Cigarettes, 5.7% THC, 0.01% CBD	300	cig
2/25/2-15	Marijuana Cigarettes, 3.0% THC, 0.10% CBD	3	cig
2/25/2-15	Marijuana Cigarettes, High Potency; 7.4% THC, 0.22% CBD	3	cig
2/25/2-15	Placebo Marijuana Cigarettes, 0.004% THC, CBD not detected	3	cig
	Pending Requests		
	Marijuana Plant Material Bulk 0.01% THC, 4.10% CBD	30	grams
	Marijuana Plant Material Bulk 0.47 % THC, 11.41 % CBD	30	grams
	Marijuana Cigarettes, 5.7% THC, 0.01% CBD	150	cig
	Placebo Marijuana Cigarettes	50	cig

Appendix C: Summary of scheduling/re-scheduling process

The process by which determinations are made with regard to scheduling or re-scheduling must go through a scientifically credible and deliberate interagency process, outlined through the graphic and text below.



Section 201(c) of the CSA requires HHS to consider eight factors as part of its scientific review:

Actual or relative potential for abuse
Scientific evidence of its pharmacological effect
State of current scientific knowledge regarding the substance
History and current pattern of abuse
Scope, duration, and significance of abuse
Risk to the public health
Psychic or physiological dependence liability
Immediate precursor of a substance already controlled

Appendix D: Guidelines for Review of Inclusion on Basis of Sex/Gender, Race, Ethnicity, and Age in Clinical Research

Office of Extramural Research
August 2014

Guidelines for the Review of Inclusion on the Basis of Sex/Gender, Race, Ethnicity, and Age in Clinical Research

Requirements and Responsibilities

As required by federal law (42 USC 289a-2) and NIH policy, applications that propose to involve human subjects must address:

1. the inclusion of women, minorities, and children in the proposed research
2. for an NIH-defined Phase III clinical trial, plans for the valid analysis of group differences on the basis of sex/gender, race, and/or ethnicity as appropriate for the scientific goals of the study.

Background Information

- Federal law requires that women and minorities be included in all clinical research studies, as appropriate for the scientific goals of the work proposed.
- Additionally, for NIH-defined Phase III clinical trials, applicants must also consider whether the study can be expected to identify potential differences by sex/gender, race, and/or ethnicity and, unless there is clear evidence that such differences are unlikely to be seen, they must include plans describing how potential group differences will be evaluated. Further information about valid analysis is available here.
- NIH policy also states that children (currently defined as persons under the age of 21) be included in human subjects research supported by NIH unless an acceptable justification for their exclusion is provided.
- Therefore, when the research involves human subjects (excluding research that qualifies for IRB exemption 4), reviewers must evaluate the proposed plans for inclusion of women, minorities, and children as one of the review criteria that factor into the evaluation of scientific and technical merit.
- **It is not expected that every study will include both sexes/genders, all racial and ethnic groups and subgroups, and children. Inclusion on the basis of sex/gender, race, and ethnicity, as well as the inclusion of children should be guided by the scientific aims of the study. Applicants should describe and justify fully the distribution of individuals that will be included in the research.**
- Policy links:
  - http://grants.nih.gov/grants/funding/women_min/women_min.htm
  - http://grants.nih.gov/grants/funding/children/children.htm

Applicant Responsibilities

Applicants must designate if human subjects are involved, and if so, whether the proposed activities meet the criteria for an IRB exemption. Applications that involve human subjects with the exception of those meeting the requirements for IRB Exemption 4 must address 1) inclusion of individuals on the basis of their sex/gender, race, and ethnicity and 2) inclusion of children (defined as persons under the age of 21). Applicants must also provide a planned enrollment table(s) with the proposed sample distributed on the basis of sex/gender, race, and ethnicity (or a cumulative inclusion enrollment report if working with an existing dataset). When conducting an NIH-defined Phase III clinical trial, applicants must also provide a description of the plans for valid analysis and evaluation of potential group differences on the basis of sex/gender, race, and ethnicity.

Scientific Review Group (SRG) Responsibilities

The NIH Peer Review regulations (42 C.F.R. 52h) specify that reviewers will take into account, in determining overall impact that the project in the application could have on the research field

involved, the adequacy of plans to include both sexes/genders, minorities, children, and special populations as appropriate for the scientific goals of the research. Therefore, the SRGs must factor their evaluation of the proposed plans for the inclusion of individuals on the basis of their sex/gender, race, ethnicity, and age into their overall evaluation of an application's scientific and technical merit.

Reviewer Responsibilities

I. Evaluate the applicant's plans for inclusion on the basis of sex/gender, race, and ethnicity

i. Does the applicant provide a description of their plans for including individuals on the basis of their sex/gender, race, and ethnicity considering the points in Section I of the Inclusion worksheet (provided below)?

If NO, rate the inclusion plans as UNACCEPTABLE.

If YES, is there an adequate justification for the proposed sample considering the required four points (see the worksheet for additional details)?

If YES, rate the inclusion plans as ACCEPTABLE.

If NO (the justification is inadequate), rate the plans as UNACCEPTABLE for the inclusion of women and minorities and EXPLAIN WHY.

ii. In addition to (i), for NIH-defined Phase III clinical trials, does the applicant address plans for a valid analysis of group differences on the basis of sex/gender, race, and/or ethnicity considering the points in Section II of the Inclusion worksheet?

If NO, rate the inclusion plans as UNACCEPTABLE [even if acceptable for (i)].

If YES, does the description of expected sex/gender, racial, and ethnic differences in intervention effect include selection and discussion of one of the required analysis plans? (see Section II of the Inclusion worksheet for details)

If the discussion is inadequate, rate the plans as UNACCEPTABLE for the inclusion of women and minorities and EXPLAIN WHY.

II. Evaluate the applicant's plans for the inclusion of children (currently defined as individuals under the age of 21)

Does the applicant provide a description of their plans for including children (currently defined as individuals under the age of 21)?

If NO, rate the inclusion plans as UNACCEPTABLE.

If YES, is there an adequate justification for the inclusion or exclusion of children considering the points in Section III of the Inclusion worksheet?

If Yes, rate the inclusion plans as ACCEPTABLE.

If NO (the justification is inadequate), rate the plans as UNACCEPTABLE for the inclusion of children and EXPLAIN WHY.

III. Prepare written comments, including specific comments describing all inclusion concerns when rated as Unacceptable.

Office of Extramural Research
August 2014

Worksheet to Assist in Reviewing the Required Points of Section on the Inclusion of Women, Minorities, and Children in Clinical Research and Clinical Trials

I. Evaluating inclusion on the basis of sex/gender, race, and ethnicity:

Point 4.2.1 Planned Distribution of Subjects

Does the applicant describe the planned distribution of subjects by sex/gender, race, and ethnicity for each proposed study considering the following?

___ Is there a description of the planned distribution using the Planned Enrollment Report format? If there is no report, does the applicant provide sufficient information to understand the planned distribution of subjects by sex/gender, race, and ethnicity?

___ For studies planning to use an existing dataset(s):
- ___ Is there a description of the planned distribution using the Planned Enrollment Report format?, or
- ___ Is there an explanation if sex/gender, racial, and/or ethnic composition of existing dataset is unknown?, if so
- ___ Is there a description of the sex/gender, racial, and ethnic composition for the population base of the existing dataset(s), if known?

Point 4.2.2 Description and Rationale of Subject Selection

Does the applicant adequately describe the subject selection criteria and rationale for selection considering the population at risk for the disease/condition under study and the scientific objectives and proposed study design?

Point 4.2.3 Rationale for Exclusion

If the proposed sample is not representative of those at risk for the disease/condition under study, does the applicant provide an adequate justification of this considering the following:
- ___ the literature on the existence of (or lack of) differences on the basis of sex/gender, race, and ethnicity
- ___ the proposed sample size
- ___ the need to fill a particular research gap
- ___ the feasibility of establishing collaborative arrangements (cost is not an acceptable justification)
- ___ the purpose of the research constrains applicant selection (e.g., unique stored specimens, rare surgical specimens etc.)

Point 4.2.4 Description of Outreach Programs for Recruitment

Does the applicant adequately describe recruitment and outreach plans or other methods for enrolling the individuals proposed as part of the sample?

II. Additional requirements when evaluating NIH-defined Phase III Clinical Trials:

Does the applicant adequately consider whether clinically important sex/gender, racial, and/or ethnic differences are expected?

Does the applicant describe one of the following?

___ Plans to conduct valid analyses to detect significant differences in intervention effect among sex/gender, racial, and/or ethnic subgroups when prior studies strongly support these significant differences among subgroups, or

___ Plans to include and analyze sex/gender, racial, and/or ethnic subgroups when prior studies strongly support no significant differences in intervention effect between subgroups. (Representation of sex/gender, racial, and ethnic groups is not required as subject selection criteria, but inclusion is encouraged), or

___ Plans to conduct valid analyses of intervention effect in sex/gender, racial and/or ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect among subgroups.

III. Evaluation inclusion of children (individuals under the age of 21):

Does the applicant adequately describe plans for the inclusion/exclusion of children (individuals under the age of 21) including:

___ Description and rationale of the age ranges of individuals expected to be recruited
___ Description and justification of the exclusion of children altogether or of a subset of children (Refer here for a complete description of justifications for excluding children)

If children are included, does the applicant adequately describe the:
___ Expertise of the investigative team for working with the children at the ages included
___ Facilities available to accommodate children
___ Inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study