DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute on Drug Abuse

Barriers to Research with Schedule I Substances

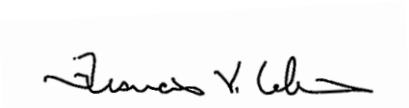

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Table of Contents

Introduction

In its conference report accompanying the fiscal year (FY) 2020 appropriations for the Departments of Defense, Labor, Health and Human Services, Education, and Related Agencies, the House Appropriations Committee requested that the National Institutes of Health (NIH) prepare and submit a brief report on barriers to research with Schedule I substances. Specifically, the report stated the following:

> *"The Committee is concerned that restrictions associated with Schedule I of the Controlled Substance Act effectively limit the amount and type of research that can be conducted on certain Schedule I drugs, especially marijuana or its component chemicals, and new synthetic drugs and analogs. At a time when we need as much information as possible about these drugs to find antidotes for their harmful effects, we should be lowering regulatory and other barriers to conducting this research. The Committee directs NIDA to provide a brief report on the barriers to research that result from the classification of drugs and compounds as Schedule I substances no later than 120 days after enactment."* (Consolidated Appropriations Act H.R.1158, page 64)

The following report has been prepared by NIH, Department of Health and Human Services (HHS), in response to this request.

Executive Summary

This document describes the scheduling process under the Controlled Substances Act, including HHS's role in the scientific and medical evaluation of substances, the process for obtaining a Schedule I research registration, and the barriers that have been reported by National Institute on Drug Abuse (NIDA)-funded researchers, which may delay or discourage research on such substances. This report also addresses specific challenges for conducting research with marijuana in light of its Schedule I status.

Background on the Scheduling Process

Drugs and other substances that are considered controlled substances under the Controlled Substances Act (CSA) are divided into five schedules. An updated and complete list of the schedules is published annually in Title 21 Code of Federal Regulations (C.F.R.) §§1308.11 through 1308.15. Substances are placed in their respective schedules based on whether they have a currently accepted medical use in treatment in the United States, their relative abuse potential, and likelihood of causing dependence when abused. Schedule I controlled substances are defined as having no currently accepted medical use in the United States, a lack of accepted safety for use under medical supervision, and a high potential for abuse.[1] Some examples of substances currently listed in Schedule I are: marijuana (cannabis), psilocybin, heroin, lysergic acid diethylamide (LSD), peyote, methaqualone, and 3,4-methylenedioxymethamphetamine

[1] https://www.deadiversion.usdoj.gov/schedules/

(known as MDMA or "Ecstasy"). Fentanyl-related substances that were not already included in Schedule I were controlled in Schedule I via a temporary scheduling order by the Drug Enforcement Administration (DEA) on Feb 6, 2018. Congress has since passed and the President has signed into law an extension of this order through May 6, 2021.

The DEA's temporary order for fentanyl-related substances is an example of CSA provisions that allow the DEA to place certain substances not already scheduled, and not subject to an approved or investigational new drug application, into Schedule I on a temporary basis to address an imminent hazard to the public health. Under these circumstances, HHS receives notice from the Attorney General (through DEA) of the proposed action. The U.S. Food and Drug Administration (FDA) then reviews the records of drugs approved or being investigated for therapeutic use, communicates the findings to the Assistant Secretary for Health (ASH), and the ASH conveys to DEA whether or not HHS has any objection to the proposed temporary order to place the substance in Schedule I.

In order for a substance to be permanently scheduled under the CSA, the FDA conducts a scientific and medical evaluation, also known as an "eight factor analysis," on the specific drug (molecule). Following consultation with NIDA, FDA makes a recommendation to the ASH on the appropriate level of permanent controls for a substance with the potential to be abused. The ASH, who has the delegated authority from the HHS Secretary for matters related to scheduling, then conveys the HHS recommendation to the DEA for action.

The CSA also allows the DEA to place certain substances not already scheduled, and not subject to an approved or investigational new drug application, into Schedule I on a temporary basis to address an imminent hazard to public health.

Process for Obtaining a Schedule I Research Registration

Obtaining or modifying a Schedule I (and, in some cases, a Schedule II-V) research registration is administratively complex. Under the law, scientists who wish to conduct research on Schedule I substances, including any substances covered by a temporary scheduling order issued by the DEA, must hold a Schedule I research registration issued by the DEA. Obtaining a Schedule I research registration is a multistep process that involves review and approval of a scientist's research protocol by multiple regulatory or review bodies, including the DEA, FDA, institutional review boards (for research with humans), and institutional animal care and use committees (for research with animals). The DEA conducts background checks on individuals who would be granted access to the substances for which a registration is sought and may perform site inspections to ensure that appropriate security safeguards are in place to mitigate against diversion. In addition to obtaining a federal Schedule I registration, researchers may be required to obtain a separate registration from their state licensing authority before their federal application can be processed.

Unlike for Schedule II-V research registration applications, FDA must review Schedule I research applications submitted to the DEA for a determination of the qualifications and competency of the researcher and the merits of the protocol. Moreover, each Schedule I substance the researcher is working on must be listed on the registration with authorized amounts the researcher can acquire for approved research. If changes are made to a DEA-registered

protocol, including changes in the amount of a substance a researcher plans to use, the amended protocol must again be submitted to the DEA and reviewed by FDA, following the same process as the original registration application. For clinical research, FDA's review is in addition to, but separate from, the review it conducts for the purposes of authorizing an investigational new drug (IND) to proceed under FDA regulations for clinical research. Authorization of the IND by FDA is required before the DEA will issue a Schedule I registration.

Challenges to Obtaining and Modifying a Schedule I Research Registration

Researchers have reported that obtaining a new registration can take more than a year, that modifying a registration can also be time consuming, and that differing interpretations of the Schedule I registration requirements among local DEA field offices, research institutions, as well as distinct federal and state registration requirements, greatly complicate the process. These challenges can impede critical research on Schedule I substances and deter or prevent scientists from pursuing such work.

As mentioned above, an overarching concern expressed by researchers is a lack of transparency regarding registration requirements for Schedule I and Schedule II-V substances, and differing interpretations of those requirements by DEA field agents and research institutions. For example, as discussed in more detail in the bullets below, whether investigators are required to stop work on newly scheduled compounds, whether the DEA permits a single investigator to hold a registration under which other investigators work, whether each research site on a single campus requires a separate registration, and the processes for obtaining a registration to work with "Code H" substances have all been sources of confusion for the research community.

Examples of specific challenges cited by members of the research community are listed below:

- Adding substances to Schedule I can lead to unexpected delays in ongoing research. Researchers working with newly scheduled compounds may have to halt work on those compounds until they obtain a Schedule I research registration or add the newly scheduled drugs to an existing Schedule I registration.
- Protocol modifications, which include adding a new drug to an existing registration, changing the quantity of a drug requested, and other deviations from the original research protocol must be submitted to and approved by the DEA. As with new registration applications, the DEA submits Schedule I protocol modifications to FDA for review prior to approval. Modifications may trigger additional inspections by the DEA, which can slow the time to approval.
- Researchers have reported that whereas it used to be common for one individual to hold a research registration under which other individuals at the same institution could work (e.g., colleagues in the same department), this is no longer the case. In some instances, separate registrations may be required for each investigator even though this is not required by federal law.
- Researchers may be required to hold separate registrations for each site at which they perform controlled substances research on a single campus. For example, a Schedule I researcher carrying out a project that involves running tests in multiple buildings may be required to obtain a separate research registration for each building.

- In cases where certain formulations or dosages of a drug are not available from licensed manufacturers, researchers may need to create them in small quantities in their laboratories. For example, marijuana extracts sometimes need to be dissolved in ethanol or oil before they can be used. There has been some uncertainty as to whether investigators holding a research registration are required to obtain a separate—and more expensive—manufacturing registration to do this. Human studies requiring the creation of final dosage formulations for administration to participants are further complicated: the DEA will not register a researcher for such work until FDA has approved an IND for the final formulation; however, the final formulation is needed in order to complete the chemistry, manufacturing and controls section required to support an IND application. In these cases, researchers are required to apply for a registration to gain access to and formulate the materials under a preclinical protocol. Once the relevant data are collected, they can submit an IND to FDA, and when the IND is authorized, they can apply for a registration (or a modification of their registration) to conduct the clinical work. This two-step process increases administrative burden on researchers and delays important clinical research.
- Some controlled substances, including the Schedule II substance carfentanil, are designated as "Code H" substances, meaning that applications to use them for research are subject to an additional administrative review by senior DEA leadership. Substances designated as Code H are not publicized, nor does the DEA publish guidance on registration requirements or review procedures for these drugs. We are aware of several researchers, including those already holding Schedule II-V registrations, who have had considerable difficulty adding carfentanil to their registrations and who were unaware that the requirements for doing so (as per their local DEA officials) differed from the requirements for other Schedule II-V substances.

Challenges Associated with Conducting Marijuana Research

The challenges associated with conducting marijuana research, which go beyond those related to the registration process, deserve separate mention in light of the increasing availability and potency of marijuana and the proliferation of new marijuana products. Research with marijuana and other Schedule I substances can only be carried out with such substances obtained from DEA-approved sources. The University of Mississippi is the only entity currently registered with the DEA to cultivate marijuana for research purposes, which it does under a contract with NIDA. This means that researchers supported by NIDA and other federal agencies are unable to use federal funds to purchase marijuana available through state marijuana dispensaries. Moreover, some universities have expressed reticence about allowing investigators to purchase dispensary products with non-federal funds or do research with these products on university grounds for fear of violating federal law. DEA has announced that it intends to license additional growers and manufacturers to increase the diversity of products and formulations available to researchers. These products may differ from the actual products being sold to consumers. The inability of researchers to access marketed products may pose barriers to studying the health effects of products that individuals are using in real-world settings.