CHAPTER 4.1-18.1
HEMP

4.1-18.1-01. Hemp (cannabis sativa L.).

"Hemp" means the plant cannabis sativa L. and any part of the plant, including the seeds and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a delta-9 tetrahydrocannabinol concentration of not more than three-tenths of one percent on a dry weight basis.

4.1-18.1-02. Hemp - Licensure.

Any person desiring to grow or process hemp shall apply to the agriculture commissioner for a license on a form prescribed by the commissioner. A license must be obtained before a person purchases or obtains hemp material for planting or propagation. The applicant is responsible for anyone working under the applicant's license for all sections of this chapter.

1. The application for a license must include the name and address of the applicant, and the legal description of the land area to be used to produce or process hemp.
2. The commissioner shall require each applicant for initial licensure to submit to a statewide and nationwide criminal history record check. The nationwide criminal history record check must be conducted in the manner provided in section 12-60-24. All costs associated with the criminal history record check are the responsibility of the applicant.
3. Criminal history records provided to the commissioner under this section are confidential. The commissioner may use the records only in determining an applicant's eligibility for licensure.
4. The commissioner shall deny licensure to any person convicted of a felony relating to a controlled substance under state or federal law in the last ten years.
5. If the applicant has completed the application process to the satisfaction of the commissioner, the commissioner shall issue the license. A license issued under this chapter expires December thirty-first.
6. An application for a license under this subsection may be submitted to the commissioner anytime before the purchase of hemp seed or viable propagation material.

4.1-18.1-03. License fee.

The commissioner shall assess each producer and processor a fee not to exceed three hundred fifty dollars. The commissioner shall deposit fees collected under this chapter in the commissioner's operating fund which are appropriated to the commissioner on a continuing basis for the purpose of enforcing this chapter.

4.1-18.1-04. License - Grounds for denial.

1. The agriculture commissioner may deny or revoke a license to any person who:
   a. Repeatedly violates this chapter;
   b. Provides false or misleading information in connection with any application required by this chapter; or
   c. Has been convicted of a felony, as described in section 4.1-18.1-02, since the most recent criminal history background check.
2. Any person denied a license under this section may request a hearing before the commissioner within thirty days after the date of the denial.

4.1-18.1-05. Violations.

1. A producer found in violation of this chapter for negligently failing to provide the legal description of the land where the producer is growing hemp, failing to obtain a license, or by producing hemp with a delta-9 tetrahydrocannabinol concentration of more than three-tenths of one percent on a dry weight basis is subject to:

a. Meeting a deadline set by the commissioner to come into compliance with this chapter; and
b. Additional reporting requirements set by the commissioner for a period of no less than two years.

2. An applicant or person licensed to grow hemp under this chapter found in violation of the chapter with a culpable mental state greater than negligence must be reported to the attorney general.

4.1-18.1-06. Confiscation and disposal.

1. Any hemp found to be in violation of this chapter is subject to confiscation and disposal by the commissioner.
2. Any disposal-related costs will be the responsibility of the producer, owner, or person responsible for the hemp.
3. The commissioner is not liable for any destruction of hemp or hemp products carried out under this chapter.

4.1-18.1-07. Commissioner powers.

The commissioner may enter on any land or areas where hemp is grown, stored, or processed for the purposes of inspections, sample collection, testing, or investigation for the purposes of enforcing this chapter.

4.1-18.1-08. Hemp - Research.

1. Any researcher associated with or operating under an institution under the control of the state board of higher education is exempt from obtaining a license described under section 4.1-18.1-02 to grow hemp. A researcher shall notify the commissioner of the researcher's intent to plant hemp and provide the following information to the commissioner:
   a. The name and contact information of the primary investigator; and
   b. The legal description of all land where hemp will be grown as part of the project.
2. The research institution shall ensure the primary investigator and all other project participants meet the criminal history background restrictions in section 4.1-18.1-02.

Rules - 2020

[Federal Register Volume 85, Number 233 (Thursday, December 3, 2020)]
[Proposed Rules]
[Pages 78047-78050]
From the Federal Register Online via the Government Publishing Office [www.gpo.gov]
[FR Doc No: 2020-26301]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-716]

Schedules of Controlled Substances: Temporary Placement of Brorphine in Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Proposed amendment; notice of intent.

SUMMARY: The Acting Administrator of the Drug Enforcement Administration is issuing this notice of intent to publish a temporary order to schedule 1-(1-(1-(4-bromophenyl)ethyl)piperidin-4-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (commonly known as brorphine), including its isomers, esters, ethers, salts, and salts of isomers, esters, and ethers whenever the existence of such isomers, esters, ethers, and salts is possible, in schedule I of the Controlled Substances Act. When it is issued, the temporary scheduling order will impose the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances on persons who handle (manufacture, distribute, reverse distribute, import, export, engage in research, conduct instructional activities or chemical analysis, or possess) or propose to handle brorphine.

DATES: December 3, 2020.

FOR FURTHER INFORMATION CONTACT: Terrence L. Boos, Drug and Chemical Evaluation Section, Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (571) 362-8207.

SUPPLEMENTARY INFORMATION: This document is issued pursuant to the temporary scheduling provisions of 21 U.S.C. 811(h). The Drug Enforcement Administration (DEA) intends to issue a temporary scheduling order (in the form of a temporary amendment) to add brorphine to schedule I under the Controlled Substances Act (CSA).\1\ The temporary scheduling order will be published in the Federal Register on or after January 4, 2021.

\1\ Though DEA has used the term "final order" with respect to temporary scheduling orders in the past, this notice of intent adheres to the statutory language of 21 U.S.C. 811(h), which refers to a "temporary scheduling order." No substantive change is intended.

Legal Authority

The CSA provides the Attorney General (as delegated to the Administrator of DEA (Administrator) pursuant to 28 CFR 0.100) with the authority to temporarily place a substance in schedule I of the CSA for two years without regard to the requirements of 21 U.S.C. 811(b), if he finds that such action is necessary to avoid an imminent hazard to the public safety. 21 U.S.C. 811(h)(1). In addition, if proceedings to control a substance are initiated under 21 U.S.C. 811(a)(1) while the substance is temporarily controlled under section 811(h), the Administrator may extend the temporary scheduling for up to one year. 21 U.S.C. 811(h)(2).

Where the necessary findings are made, a substance may be temporarily scheduled if it is not listed in any other schedule under 21 U.S.C. 812, or if there is no exemption or approval in effect for the substance under section 505 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355. 21 U.S.C. 811(h)(1); 21 CFR part 1308.

Background

Section 811(h)(4) requires the Administrator to notify the Secretary of the Department of Health and Human Services (HHS) of his intention to temporarily place a substance in schedule I of the CSA.\2\ The Acting Administrator transmitted notice of his intent to place brorphine in schedule I on a temporary basis to the Assistant Secretary for Health of HHS (Assistant Secretary) by letter dated September 22, 2020. The Assistant Secretary responded to this notice by letter dated October 27, 2020, and advised that based on a review by the Food and Drug Administration (FDA), there are currently no investigational new drug applications or approved new drug applications for brorphine. The Assistant Secretary also stated that HHS had no objection to the temporary placement of brorphine in schedule I of the CSA. Brorphine is not currently listed in any schedule under the CSA, and no exemptions or approvals are in effect for brorphine under 21 U.S.C. 355.

\2\ The Secretary of HHS has delegated to the Assistant Secretary for Health of HHS the authority to make domestic drug scheduling recommendations. 58 FR 35460, July 1, 1993.

To find that placing a substance temporarily in schedule I of the CSA is necessary to avoid an imminent hazard to the public safety, the Administrator is required to consider three of the eight factors set forth in 21 U.S.C. 811(c): The substance's history and current pattern of abuse; the scope, duration and significance of abuse; and what, if any, risk there is to the public health. 21 U.S.C. 811(h)(3). Consideration of these factors includes actual abuse; diversion from legitimate channels; and clandestine importation, manufacture, or distribution. 21 U.S.C. 811(h)(3).

A substance meeting the statutory requirements for temporary scheduling may only be placed in schedule I. 21 U.S.C. 811(h)(1). 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).

Brorphine

The availability of synthetic opioids on the illicit drug market continues to pose an imminent hazard to the public safety. Adverse health effects associated with the abuse of synthetic opioids and the increased popularity of these substances have been serious concerns in recent years. The presence of new synthetic opioids with no approved medical use exacerbates the unprecedented opioid epidemic the United States continues to experience. The trafficking and abuse of new synthetic opioids are deadly new trends.

The identification of brorphine on the illicit drug market has been reported in the United States, Canada, Belgium, and Sweden. Data obtained from preclinical pharmacology studies show that brorphine has a pharmacological profile similar to that of other potent opioids such as morphine and fentanyl, schedule II controlled substances. Because of the pharmacological similarities between brorphine and other potent opioids, the use of brorphine presents a high risk of abuse and may negatively affect users and their communities. The positive identification of this substance in law enforcement seizures and post-mortem toxicology reports is a serious concern to the public safety. The abuse of brorphine has been associated with at least seven fatalities between June 2020 and July 2020 in the United States. Thus, brorphine poses an imminent hazard to public safety.

Available data and information for brorphine, as summarized below, indicates that this substance has 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. DEA's three-factor analysis is available in its entirety under "Supporting and Related Material" of the public docket for this action at www.regulations.gov under Docket Number DEA-716.

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Factor 4. History and Current Pattern of Abuse

Brorphine is part of a structural class of compounds known as substituted piperidine benzimidazolones. The general synthesis of brorphine was first reported in the literature in 2018. Brorphine is not an approved pharmaceutical product and is not approved for medical use anywhere in the world. The Assistant Secretary, by a letter to DEA dated October 27, 2020, stated that there are no FDA-approved new drug applications or investigational new drug applications for brorphine in the United States; hence, there is no legitimate channel for brorphine as a marketed drug product. The appearance of brorphine on the illicit drug market is similar to other designer drugs trafficked for their psychoactive effects.

Since 2014, numerous synthetic opioids structurally related to fentanyl and several synthetic opioids from other structural classes have begun to emerge on the illicit drug market as evidenced by the identification of these drugs in forensic drug exhibits and toxicology samples. Beginning in June 2019, brorphine emerged in the U.S. illicit, synthetic drug market as evidenced by brorphine's identification in drug seizures. Between July and September of 2019, brorphine was first reported in drug casework in Canada and was first reported in police seizures in Sweden in March 2020.\3\

\3\ Health Canada Drug Analysis Service (2019); Analyzed Drug Report Canada 2019--Q3 (July to September); European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2020); EU Early Warning System Situation Report, Situation report 1--June 2020.

Brorphine has been encountered by U.S. law enforcement in powder form. In the United States, brorphine has been identified as a single substance and in combination with other substances. Twenty reports of brorphine have been reported in the National Forensic Laboratory Information System (NFLIS) in 2019 and 2020 from three different states (see Factor 5).\4\ In several NFLIS encounters, brorphine was found in combination with heroin (a schedule I substance) and fentanyl (a schedule II substance). In reports from the Northeastern Illinois Regional Crime Laboratory, suspected heroin/fentanyl powders were analyzed and found to be brorphine in combination with flualprazolam, a non-scheduled benzodiazepine, and diphenhydramine, an over-the-counter antihistamine.\5\

\4\ NFLIS represents an important resource in monitoring illicit drug trafficking, including the diversion of legally manufactured pharmaceuticals into illegal markets. NFLIS-Drug is a comprehensive information system that includes data from forensic laboratories that handle the nation's drug analysis cases. NFLIS-Drug participation rate, defined as the percentage of the national drug caseload represented by laboratories that have joined NFLIS, is currently 98.5 percent. NFLIS includes drug chemistry results from completed analyses only. While NFLIS data is not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. See 76 FR 77330, 77332, December 12, 2011. NFLIS data was queried on August 18, 2020.

\5\ Email communications with Northeastern Illinois Regional Crime Laboratory, dated 7/1/2020 and 6/11/2020.

Post-mortem toxicology samples collected and submitted to National Medical Services (NMS) Laboratory \6\ in June and July 2020 verified the appearance of brorphine. Brorphine was first reported by the Center for Forensic Science Research and Education (CFSRE)--Novel Psychoactive Substance (NPS) Discovery Program (under the novel psychoactive substances discovery program, in collaboration with NMS Labs) in July 2020. In seven post-mortem toxicology reports in June 2020 and July 2020, brorphine was found in combination with fentanyl, flualprazolam, and heroin. Evidence suggests that individuals are using brorphine as a replacement to heroin or other opioids, either knowingly or unknowingly.

\6\ NMS Labs, in collaboration with the Center for Forensic Science Research and Education at the Fredric Rieders Family Foundation and the Organized Crime Drug Enforcement Task Force at the United States Department of Justice, has received funding from the Centers for Disease Control and Prevention to develop systems for the early identification and notification of novel psychoactive substances in the drug supply within the United States.

Factor 5. Scope, Duration, and Significance of Abuse

Brorphine has been described as a potent synthetic opioid and evidence suggests it is being abused for its opioidergic effects (see Factor 6). According to a recent publication by CFSRE--NPS Discovery, brorphine has been positively identified in seven death investigation cases spanning between June 2020 and July 2020. These cases correspond to three states--Illinois (3), Minnesota (3), and Arizona (1). Most (n = 6) of the decedents were male. The decedents' ages ranged between 40's and 60's with an average age of 52 years. Other substances identified in postmortem blood specimens obtained from these decedents include flualprazolam, a nonscheduled benzodiazepine (n = 5), fentanyl, a schedule II substance (n = 7), and heroin, a schedule I substance (n = 4). The appearance of benzodiazepines and other opioids is common with polysubstance abuse.

NFLIS registered 20 reports of brorphine from Ohio (4), Pennsylvania (1), and Wisconsin (15) in 2019 and 2020. NFLIS was queried on August 18, 2020, for brorphine. Due to the rapid appearance of the drug, brorphine is most likely under reported as forensic laboratories secure reference standards for the confirmative identification and reporting of this substance.

The population likely to abuse brorphine appears to be the same as those abusing prescription opioid analgesics, heroin, tramadol, fentanyl, and other synthetic opioid substances. This is evidenced by the types of other drugs co-identified in samples obtained from brorphine seizures and post-mortem toxicology reports. Because abusers of brorphine are likely to obtain it through unregulated sources, the identity, purity, and quantity of brorphine are uncertain and inconsistent, thus posing significant adverse health risks to the end user. The misuse and abuse of opioids have been demonstrated and are well-characterized. According to the most recent data from the National Survey on Drug Use and Health (NSDUH),\7\ as of 2018, an estimated 10.3 million people aged 12 years or older misused opioids in the past year, including 9.9 million prescription pain reliever misusers and 808,000 heroin users. In 2018, an estimated 2 million people had an opioid use disorder which included 1.7 million people with a prescription pain reliever use disorder and 500,000 people with heroin use disorder. This population abusing opioids is likely to be at risk of abusing brorphine. Individuals who initiate use (i.e., use a drug for the first time) of brorphine are likely to be at risk of developing substance use disorder, overdose, and death similar to that of other opioid analgesics (e.g., fentanyl, morphine, etc.). Law enforcement reports demonstrate that brorphine is being illicitly distributed and abused.

\7\ The National Survey on Drug Use and Health (NSDUH), formerly known as the National Household Survey on Drug Abuse (NHSDA), is conducted annually by the Department of Health and Human Services Substance Abuse and Mental Health Services Administration (SAMHSA). It is the primary source of estimates of the prevalence and incidence of nonmedical use of pharmaceutical drugs, illicit drugs, alcohol, and tobacco use in the United States. The survey is based on a nationally representative sample of the civilian, non-institutionalized population 12 years of age and older. The survey excludes homeless people who do not use shelters, active military personnel, and residents of institutional group quarters such as jails and hospitals. The NSDUH provides yearly national and state level estimates of drug abuse, and includes prevalence estimates by lifetime (i.e., ever used), past year, and past month abuse or dependence.

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Factor 6. What, if Any, Risk There Is to the Public Health

The increase in opioid overdose deaths in the United States has been exacerbated recently by the availability of potent synthetic opioids on the illicit drug market. Data obtained from pre-clinical studies demonstrate that brorphine exhibits a pharmacological profile similar to that of other mu ([micro])-opioid receptor agonists. Data from in vitro studies completed in 2020 showed that brorphine binds to and activates the [micro]-opioid receptors. In the [\35\S]GTP[gamma]S cell-based receptor assay, brorphine, similar to fentanyl, acted as a [micro]-opioid receptor agonist. Brorphine's activation of [micro]-opioid receptor was also shown to involve recruitment of beta-arrestin-2, a regulatory protein whose interaction with the [micro]-opioid receptor has been implicated in the adverse effects of [micro]-opioid receptor activation. Brorphine binds to and activates the [micro]-opioid receptor and has efficacy on scale with fentanyl. It is well established that substances that act as [micro]-opioid receptor agonists have a high potential for addiction and can induce dose-dependent respiratory depression.

As with any [micro]-opioid receptor agonist, the potential health and safety risks for users of brorphine are high. The public health risks associated to the abuse of heroin and other [micro]-opioid receptor agonists are well established and have resulted in large numbers of drug treatment admissions, emergency department visits, and fatal overdoses. According to the Centers for Disease Control and Prevention (CDC), opioids, mainly synthetic opioids other than methadone, are predominantly responsible for drug overdose deaths in recent years. A CDC report shows that, from 2013 to 2018, opioid-related overdose deaths in the United States increased from 25,052 to 46,802. Of the drug overdose deaths for 2018, opioids were involved in about 69.5 percent of all drug-involved overdose deaths.

In the United States, the abuse of opioid analgesics has resulted in large numbers of treatment admissions, emergency department visits, and fatal overdoses. The introduction of potent synthetic opioids such as brorphine into the illicit market may serve as a portal to problematic opioid use for those seeking these powerful opioids.

Brorphine has been co-identified with other substances in seven post-mortem toxicology cases in June and July of 2020. These substances include other opioids such as fentanyl and heroin, and other substance classes such as benzodiazepines. These deaths occurred in three states: Illinois, Arizona, and Minnesota. Information gathered from case history findings shows that brorphine use is similar to that of classic opioid agonists. As documented by toxicology reports, poly-substance abuse remains common in fatalities associated with the abuse of brorphine.

Finding of Necessity of Schedule I Placement To Avoid Imminent Hazard to Public Safety

In accordance with **21 U.S.C. 811(h)(3)**, based on the available data and information summarized above, the uncontrolled manufacture, distribution, reverse distribution, importation, exportation, conduct of research and chemical analysis, possession, and abuse of brorphine pose an imminent hazard to the public safety. DEA is not aware of any currently accepted medical uses for brorphine in the United States. A substance meeting the statutory requirements for temporary scheduling, found in **21 U.S.C. 811(h)(1)**, may only be placed in schedule I. 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. Available data and information for brorphine indicate that this substance has 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. As required by **21 U.S.C. 811(h)(4)**, the Acting Administrator, through a letter dated September 22, 2020, notified the Assistant Secretary of DEA's intention to temporarily place brorphine in schedule I.

Conclusion

This notice of intent provides the 30-day notice pursuant to **21 U.S.C. 811(h)(1)** of DEA's intent to issue a temporary scheduling order. In accordance with **21 U.S.C. 811(h)(1)** and (3), the Acting Administrator considered available data and information, herein set forth the grounds for his determination that it is necessary to temporarily schedule brorphine in schedule I of the CSA, and finds that placement of this substance in schedule I of the CSA is necessary in order to avoid an imminent hazard to the public's safety.

The temporary placement of brorphine in schedule I of the CSA will take effect pursuant to a temporary scheduling order, which will not be issued before January 4, 2021. Because the Acting Administrator hereby finds that it is necessary to temporarily place brorphine in schedule I to avoid an imminent hazard to the public safety, the temporary order scheduling this substance will be effective on the date the order is published in the Federal Register, and will be in effect for a period of two years, with a possible extension of one additional year, pending completion of the regular (permanent) scheduling process. **21 U.S.C. 811(h)(1)** and **(2)**. It is the intention of the Acting Administrator to issue a temporary scheduling order as soon as possible after the expiration of 30 days from the date of publication of this document. Upon publication of the temporary order, brorphine will then be subject to the CSA's schedule I regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, reverse distribution, importation, exportation, research, conduct of instructional activities and chemical analysis, and possession.

The CSA sets forth specific criteria for scheduling a drug or other substance. Regular scheduling actions in accordance with **21 U.S.C. 811(a)** are subject to formal rulemaking procedures done "on the record after opportunity for a hearing" conducted pursuant to the provisions of 5 U.S.C. 556 and 557. **21 U.S.C. 811.** The regular scheduling process of formal rulemaking affords interested parties with appropriate process and the government with any additional relevant information needed to make a determination. Final decisions that conclude the regular scheduling process of formal rulemaking are subject to judicial review. **21 U.S.C. 877.** Temporary scheduling orders are not subject to judicial review. 21 U.S.C. 811(h)(6).

Regulatory Analyses

The CSA provides for a temporary scheduling action where such action is necessary to avoid an imminent hazard to the public safety. **21 U.S.C. 811(h)(1)**. As provided in this subsection, the Administrator (as delegated by the Attorney General) may, by order, schedule a substance in schedule I on a temporary basis. Such an order may not be issued before the expiration of 30 days from: (1) The publication of a notice in the Federal Register of the intention to issue such order and the grounds upon which such order is to be issued, and (2) the date that notice of the proposed temporary scheduling order is transmitted to the Secretary of HHS.

Inasmuch as **21 U.S.C. 811(h)(1)** directs that temporary scheduling actions be issued by order and sets forth the procedures by which such orders are to be issued, including the requirement

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of a publication in the Federal Register of a notice of intent, the notice-and-comment requirements of section 553 of the Administrative Procedure Act (APA), 5 U.S.C. 553, do not apply to this notice of intent. The APA expressly differentiates between an order and a rule, as it defines an "order" to mean a "final disposition, whether affirmative, negative, injunctive, or declaratory in form, of an agency in a matter other than rule making." 5 U.S.C. 551(6) (emphasis added). The specific language chosen by Congress indicates an intention for DEA to proceed through the issuance of an order instead of proceeding by rulemaking. Given that Congress specifically requires the Administrator to follow rulemaking procedures for other kinds of scheduling actions, see **21 U.S.C. 811(a)**, it is noteworthy that, in 21 U.S.C. 811(h)(1), Congress authorized the issuance of temporary scheduling actions by order rather than by rule.

In the alternative, even assuming that this notice of intent might be subject to section 553 of the APA, the Acting Administrator finds that there is good cause to forgo the notice-and-comment requirements of section 553, as any further delays in the process for issuance of temporary scheduling orders would be impracticable and contrary to the public interest in view of the manifest urgency to avoid an imminent hazard to the public safety.

Although DEA believes this notice of intent to issue a temporary scheduling order is not subject to the notice-and-comment requirements of section 553 of the APA, DEA notes that in accordance with **21 U.S.C. 811(h)(4)**, the Acting Administrator took into consideration comments submitted by the Assistant Secretary in response to the notice that DEA transmitted to the Assistant Secretary pursuant to such subsection.

Further, DEA believes that this temporary scheduling action is not a "rule" as defined by 5 U.S.C. 601(2), and, accordingly, is not subject to the requirements of the Regulatory Flexibility Act. The requirements for the preparation of an initial regulatory flexibility analysis in 5 U.S.C. 603(a) are not applicable where, as here, DEA is not required by section 553 of the APA or any other law to publish a general notice of proposed rulemaking.

In accordance with the principles of Executive Orders (E.O.) 12866, 13563, and 13771, this notice of intent is not a significant regulatory action. E.O. 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, if regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health, and safety effects; distributive impacts; and equity). E.O. 13563 is supplemental to and reaffirms the principles, structures, and definitions governing regulatory review as established in E.O. 12866. E.O. 12866 classifies a "significant regulatory action," requiring review by the Office of Management and Budget (OMB), as any regulatory action that is likely to result in a rule that may: (1) Have an annual effect on the economy of $100 million or more or adversely affect in a material way the economy; a sector of the economy; productivity; competition; jobs; the environment; public health or safety; or State, local, or tribal governments or communities; (2) create a serious inconsistency or otherwise interfere with an action taken or planned by another agency; (3) materially alter the budgetary impact of entitlements, grants, user fees, or loan programs, or the rights and obligations of recipients thereof; or (4) raise novel legal or policy issues arising out of legal mandates, the President's priorities, or the principles set forth in the Executive Order. Because this is not a rulemaking action, this is not a significant regulatory action as defined in Section 3(f) of E.O. 12866. In addition, this action does not meet the definition of an E.O. 13771 regulatory action, and the repeal and cost offset requirements of E.O. 13771 have not been triggered.

This action will not have substantial direct effects on the states, on the relationship between the national government and the states, or on the distribution of power and responsibilities among the various levels of government. Therefore, in accordance with E.O. 13132 (Federalism), it is determined that this action does not have sufficient federalism implications to warrant the preparation of a Federalism Assessment.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, DEA proposes to amend 21 CFR part 1308 as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

- 1. The authority citation for part 1308 continues to read as follows:

  Authority: 21 U.S.C. 811, 812, 871(b), 956(b), unless otherwise noted.

- 2. In **Sec. 1308.11**, add paragraph (h)(49) to read as follows:

Sec. 1308.11 Schedule I

* * * * *

(h) * * *

(49) 1-(1-(1-(4-bromophenyl)ethyl)piperidin-4-yl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one, its isomers, esters, ethers, salts and salts of isomers, esters and ethers (Other names: brorphine; 1-[1-[1-(4-bromophenyl)ethyl]-4-piperidinyl]-1,3-dihydro-2*H*benzimidazol-2-one)	9098

* * * * *

Timothy J. Shea,
Acting Administrator.

Rules - 2020

[Federal Register Volume 85, Number 162 (Thursday, August 20, 2020)]
[Rules and Regulations]
[Pages 51342-51346]
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[FR Doc No: 2020-17951]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-631]

Schedules of Controlled Substances: Temporary Placement of Isotonitazene in Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Temporary amendment; temporary scheduling order.

SUMMARY: The Acting Administrator of the Drug Enforcement Administration is issuing this temporary order to schedule N,N-diethyl-2-(2-(4 isopropoxybenzyl)-5-nitro-1H-benzimidazol-1-yl)ethan-1-amine (commonly known as isotonitazene), including its isomers, esters, ethers, salts, and salts of isomers, esters, and ethers whenever the existence of such isomers, esters, ethers, and salts is possible, in schedule I. This action is based on a finding by the Acting Administrator that the placement of isotonitazene in schedule I of the Controlled Substances Act is necessary to avoid an imminent hazard to the public safety. As a result of this order, the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances will be imposed on persons who handle (manufacture, distribute, reverse distribute, import, export, engage in research, conduct instructional activities or chemical analysis with, or possess), or propose to handle isotonitazene.

DATES: This temporary scheduling order is effective August 20, 2020, until August 20, 2022. If this order is extended or made permanent, DEA will publish a document in the Federal Register.

FOR FURTHER INFORMATION CONTACT: Scott A. Brinks, Regulatory Drafting and Policy Support Section, Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (571) 362-3261.

SUPPLEMENTARY INFORMATION:

Legal Authority

The Controlled Substances Act (CSA) provides the Attorney General with the authority to temporarily place a substance in schedule I of the CSA for two years without regard to the requirements of **21 U.S.C. 811**(b), if he finds that such action is necessary to avoid an imminent hazard to the public safety. 21 U.S.C. 811(h)(1). In addition, if proceedings to control a substance permanently are initiated under 21 U.S.C. 811(a)(1) while the substance is temporarily controlled under section 811(h), the Attorney General may extend the temporary scheduling \1\ for up to one year. 21 U.S.C. 811(h)(2).

\1\ Though the Drug Enforcement Administration (DEA) has used the term "final order" with respect to temporary scheduling orders in the past, this document adheres to the statutory language of **21 U.S.C. 811**(h), which refers to a "temporary scheduling order." No substantive change is intended.

Where the necessary findings are made, a substance may be temporarily scheduled if it is not listed in any other schedule under section 202 of the CSA, **21 U.S.C. 812**, or if there is no exemption or approval in effect for the substance under section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. 355. **21 U.S.C. 811**(h)(1); 21 CFR part 1308. The Attorney General has delegated scheduling authority under 21 U.S.C. 811 to the Administrator of DEA (Administrator). 28 CFR 0.100.

Background

21 U.S.C. 811(h)(4) requires the Administrator to notify the Secretary of the Department of Health and Human Services (HHS) of his intention to temporarily place a substance in schedule I of the CSA.\2\ The Acting Administrator transmitted notice of his intent to place isotonitazene in schedule I on a temporary basis to the Assistant Secretary for Health of HHS (Assistant Secretary) by letter dated March 2, 2020. The Assistant Secretary responded to this notice by letter dated March 31, 2020, and advised that based on a review by the Food and Drug Administration (FDA), there are currently no investigational new drug applications (INDs) or approved new drug applications (NDAs) for isotonitazene. The Assistant Secretary also stated that HHS had no objection to the temporary placement of isotonitazene in schedule I of the CSA.

\2\ The Secretary of HHS has delegated to the Assistant Secretary for Health of HHS the authority to make domestic drug scheduling recommendations. 58 FR 35460, July 1, 1993.

The Drug Enforcement Administration (DEA) has taken into consideration the Assistant Secretary's comments as required by **21 U.S.C. 811**(h)(4). Isotonitazene is not currently listed in any schedule under the CSA, and no exemptions or approvals are in effect for isotonitazene under section 505 of the FDCA, 21 U.S.C. 355. DEA has found that the control of isotonitazene in schedule I on a temporary basis is necessary to avoid an imminent hazard to the public safety.

As required by **21 U.S.C. 811**(h)(1)(A), DEA published a notice of intent to temporarily schedule isotonitazene in the Federal Register on June 18, 2020. 85 FR 38619. That notice of intent discussed findings from DEA's three-factor analysis dated May 2020, which DEA made available on www.regulations.gov contemporaneously with the publication of the notice of intent. This temporary scheduling order discusses updated findings on isotonitazane for one of the three factors (Factor 5) in DEA's July 2020 analysis related to law enforcement seizures, overdoses, and regulatory status.

To find that placing a substance temporarily in schedule I of the CSA is necessary to avoid an imminent hazard to the public safety, the Administrator is required to consider three of the eight factors set forth in **21 U.S.C. 811**(c): The substance's history and current pattern of abuse; the scope, duration, and significance of abuse; and what, if any, risk there is to the public health. 21 U.S.C. 811(h)(3). Consideration of these factors includes actual abuse, diversion from legitimate channels, and clandestine importation, manufacture, or distribution. 21 U.S.C. 811(h)(3).

A substance meeting the statutory requirements for temporary scheduling may only be placed in schedule I. **21 U.S.C. 811(h)(1).** 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).**

Available data and information for isotonitazene summarized below indicate that it has 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. DEA's May and July 2020 three-factor analyses and the Assistant Secretary's March 31, 2020, letter are available in their entirety under the tab "Supporting Documents" of the public docket of this action at www.regulations.gov.

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Isotonitazene

The availability of synthetic opioids in the illicit drug market continues to pose an imminent hazard to the public safety. Adverse health effects associated with the abuse of synthetic opioids and the continued evolution and increased popularity of these substances have been a serious concern in recent years. As the United States continues to experience an unprecedented epidemic of opioid misuse and abuse, the presence of new synthetic opioids with no approved medical use exacerbates the epidemic. The trafficking and abuse of new synthetic opioids are deadly new trends.

The identification of isotonitazene, chemically known as N,N-diethyl-2-(2-(4 isopropoxybenzyl)-5-nitro-1H-benzimidazol-1-yl)ethan-1-amine (other name: N,N-diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine), in the illicit drug market has been reported in Canada, Estonia, Germany, Latvia, Sweden, and the United States (see Factor 4 below). Data obtained from preclinical pharmacology studies shows that isotonitazene has a pharmacological profile similar to that of the potent synthetic opioid etonitazene, a schedule I controlled substance. Because of the pharmacological similarities of isotonitazene to etonitazene, the use of isotonitazene presents a high risk of abuse and may negatively affect users and communities. The abuse of isotonitazene has been associated with at least 19 fatalities in the United States (see Factor 5 below). The positive identification of this substance in overdose and post-mortem cases is a serious concern for public safety. Thus, isotonitazene poses an imminent hazard to public safety.

Available data and information for isotonitazene, as summarized below, indicates that this substance has 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. DEA's three-factor analysis is available in its entirety under "Supporting and Related Material" of the public docket for this action at www.regulations.gov under Docket Number DEA-631.

Factor 4. History and Current Pattern of Abuse

The chemical syntheses of isotonitazene (a benzimidazole derivative) and other benzimidazole derivatives (including schedule I substances such as synthetic opioids etonitazene and clonitazene) were first reported in the scientific literature in 1957. Isotonitazene is not an approved pharmaceutical product and is not approved for medical use anywhere in the world. As discussed in the background section, the Assistant Secretary stated in a March 31, 2020, letter to DEA that there are no INDs or FDA-approved NDAs for isotonitazene in the United States. Hence, DEA notes there is no legitimate channel for isotonitazene as a marketed drug product.

Since 2014, numerous synthetic opioids structurally related to fentanyl and several opioids from other structural classes have begun to emerge in the illicit drug market, as evidenced by the identification of these drugs in forensic drug exhibits and toxicology samples. Beginning in April 2019, isotonitazene emerged on the illicit synthetic drug market in the United States, as evidenced by its identification in drug seizures and in biological samples collected and submitted to National Medical Services (NMS) Laboratory \3\ in August 2019. In August 2019, isotonitazene was first reported in a drug case in Belgium and in toxicology casework in Canada (a toxicological sample was collected in March 2019). In the United States, the Center for Forensic Science Research and Education (under the novel psychoactive substances discovery program) first reported isotonitazene in November 2019.

\3\ NMS Labs, in collaboration with the Center for Forensic Science Research and Education at the Fredric Rieders Family Foundation and the Organized Crime Drug Enforcement Task Force at the U.S. Department of Justice, has received funding from the Centers for Disease Control and Prevention to develop systems for the early identification and notification of novel psychoactive substances in the drug supply within the United States.

According to a report by the European Monitoring Center for Drugs and Drug addiction and Europol,\4\ between April 2019 and January 2020, four member-states (Estonia, Latvia, Germany, and Sweden) have reported 24 isotonitazene cases involving 109.6 grams of powder (22 cases) and 4.5 grams of liquid (two cases). Isotonitazene has been encountered by United States law enforcement primarily in powder form. In March 2020, Canada law enforcement also encountered isotonitazene in a tablet form, as a white triangular tablet with 'M' logo on one side and '8' logo on the other side, and as a blue tablet in Dilaudid counterfeit pills. Identification of isotonitazene in counterfeit pills is deeply concerning because the identity, purity, and quantity of isotonitazene in this formulation are uncertain, thus presenting additional safety concerns for unsuspecting users.

\4\ European Monitoring Centre for Drugs and Drug Addiction and Europol (2020), EMCDDA initial report on the new psychoactive substance N,N-diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine (isotonitazene). In accordance with Article 5b of Regulation (EC) No 1920/2006 (as amended), Publications Office of the European Union, Luxembourg.

In the United States, isotonitazene has been identified as a single substance or in combination with other substances. In April 2019, the United States Customs and Border Protection (CBP) seized 1.6 grams of isotonitazene in California. In addition, Wisconsin State Crime Laboratories identified isotonitazene mixed with heroin and bromazolam, a nonscheduled benzodiazepine, in seized powder. Further, isotonitazene was identified in a substance obtained from the scene of a death investigation in Iowa. Evidence suggests that individuals are using isotonitazene as a replacement to heroin or other opioids, either knowingly or unknowingly.

Factor 5. Scope, Duration, and Significance of Abuse

Isotonitazene, similar to etonitazene (schedule I), has been described as a potent synthetic opioid and evidence suggests it is being abused for its opioidergic effects (see Factor 6). The abuse of isotonitazene, similar to other synthetic opioids, has resulted in adverse health effects. Isotonitazene has been positively identified in 18 death investigations between August 2019 and January 2020. These reports were from four states--Illinois (9), Indiana (7), Minnesota (1), and Wisconsin (1). Most (n = 12) of the decedents were male. The ages ranged from 24 to 66 years old with an average age of 41. Other substances identified in postmortem blood specimens obtained from these decedents include etizolam (6); flualprazolam, a nonscheduled benzodiazepine (7); fentanyl (6); heroin (3); tramadol, a schedule IV narcotic (2); and U-47700, a schedule I synthetic opioid (1). The average concentration of isotonitazene in these biological samples (blood) was 2.2 2.1 nanogram/milliliter (ng/ml) (range 0.4 to 9.5 ng/ml). Isotonitazene was detected as the only opioid in 50 percent (n = 9) of the specimens for these decedents. DEA \5\ is aware of another postmortem case that occurred in January 2020 in Pennsylvania where isotonitazene was identified in a biological sample. In total, isotonitazene has been positively identified in 19 postmortem cases.

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Recent communication from Minnesota Department of Health \6\ reports the positive identification of isotonitazene in two overdose cases.

\5\ Email communication from DEA Philadelphia Field Division on March 4, 2020.

\6\ Email communication from Minnesota Department of Health: Biomonitoring and Emerging Contaminants Unit; received May 26, 2020.

Law enforcement data indicate that isotonitazene has appeared in the United States' illicit drug market. According to the National Forensic Laboratory Information System (NFLIS) \7\ database, which collects drug identification results from drug cases submitted to and analyzed by Federal, State, and local forensic laboratories, there have been 48 encounters of isotonitazene in the United States (queried May 14, 2020). These 48 encounters occurred in 2019 and 2020 in five states: California (1), Iowa (5), Ohio (4), Tennessee (13), and Wisconsin (25). One of these encounters consisted of 1.6 grams of isotonitazene seized by the CBP in California in April 2019.

\7\ NFLIS represents an important resource in monitoring illicit drug trafficking, including the diversion of legally manufactured pharmaceuticals into illegal markets. NFLIS-Drug is a comprehensive information system that includes data from forensic laboratories that handle the nation's drug analysis cases. NFLIS-Drug participation rate, defined as the percentage of the national drug caseload represented by laboratories that have joined NFLIS, is currently 98.5 percent. NFLIS includes drug chemistry results from completed analyses only. While NFLIS data is not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. See 76 FR 77330, 77332, Dec. 12, 2011. NFLIS data was queried on May 14, 2020.

As of May 2020, Ohio and Wisconsin enacted emergency legislation to control isotonitazene as a schedule I controlled substance. Internationally, isotonitazene is controlled under Estonia, Latvia, Poland, and Sweden drug control legislation. In the United Kingdom, isotonitazene is controlled under the Psychoactive Substances Act 2016. Further, isotonitazene is controlled under the Norwegian Medicines Act and Lithuania medicine legislation.\8\

\8\ The Medicines Act, LOVDATA, https://lovdata.no/dokument/NL/lov/1992-12-04-132, 1992.

The population likely to abuse isotonitazene appears to be the same as those abusing prescription opioid analgesics, heroin, tramadol, fentanyl, and other synthetic opioid substances. This is evidenced by the types of other drugs co-identified in isotonitazene fatal overdose cases. Because abusers of isotonitazene are likely to obtain it through unregulated sources, the identity, purity, and quantity are uncertain and inconsistent, thus posing significant adverse health risks to the end user. The misuse and abuse of opioids have been demonstrated and are well characterized. According to the most recent data from the National Survey on Drug Use and Health (NSDUH),\9\ as of 2018, an estimated 10.3 million people aged 12 years or older had misused opioids in the past year, including 9.9 million prescription pain reliever misusers and 808,000 heroin users. In 2018, an estimated 2.0 million people had an opioid use disorder which included 1.7 million people with a prescription pain reliever use disorder and 0.5 million people with heroin use disorder. This population abusing opioids is likely to be at risk of abusing isotonitazene. Individuals who initiate (i.e., use a drug for the first time) use of isotonitazene are likely to be at risk of developing substance use disorders, overdoses, and death similar to that of other opioid analgesics (e.g., fentanyl, morphine, etc.). Law enforcement and toxicology reports demonstrate that isotonitazene is being illicitly distributed and abused.

\9\ The National Survey on Drug Use and Health (NSDUH), formerly known as the National Household Survey on Drug Abuse (NHSDA), is conducted annually by HHS' Substance Abuse and Mental Health Services Administration (SAMHSA). It is the primary source of estimates of the prevalence and incidence of nonmedical use of pharmaceutical drugs, illicit drugs, alcohol, and tobacco use in the United States. The survey is based on a nationally representative sample of the civilian, non-institutionalized population twelve years of age and older. The survey excludes homeless people who do not use shelters, active military personnel, and residents of institutional group quarters such as jails and hospitals. The NSDUH provides yearly national and state level estimates of drug abuse, and includes prevalence estimates by lifetime (i.e., ever used), past year, and past month abuse or dependence. The 2018 NSDUH annual report is available at https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHNationalFindingsReport2018/NSDUHNationalFindingsReport2018.pdf (last accessed June 18, 2020).

Factor 6. What, If Any, Risk There Is to the Public Health

The increase in opioid overdose deaths in the United States has been exacerbated recently by the availability of potent synthetic opioids in the illicit drug market. Data obtained from pre-clinical studies demonstrate that isotonitazene exhibits a pharmacological profile similar to that of etonitazene and other mu-opioid receptor agonists. In an in vivo (in mice) study, isotonitazene was 500 times more potent than morphine as an analgesic in a tail-flick assay. The tail-flick assay is useful in evaluating antinociceptive effect. Data from in vitro studies showed that isotonitazene activated the mu-opioid receptor and acted as a mu-opioid receptor agonist. Isotonitazene, similar to hydromorphone and fentanyl, activated the mu-opioid receptor and acted as an agonist via interaction at the mu-opioid receptor with [beta]-arrestin-2, a regulatory protein, in a live cell-based receptor assay. Naloxone, an opioid receptor antagonist, blocked isotonitazene's activation of the mu-opioid receptor. Substances that act as an agonist at the mu-opioid receptors have a high potential for addiction and can induce dose-dependent respiratory depression.

As with any mu-opioid receptor agonist, the potential health and safety risks for users are high. The public health risks attendant to the abuse of heroin and other mu-opioid receptor agonists are well established and have resulted in large numbers of drug treatment admissions, emergency department visits, and fatal overdoses. According to the Centers for Disease Control and Prevention (CDC), opioids, mainly synthetic opioids other than methadone, are predominantly responsible for drug overdose deaths in recent years. A CDC report shows that from 2013 to 2018,\10\ opioid-related overdose deaths in the United States increased from 25,052 to 46,802. Of the drug overdose death data for 2018, opioids were involved in about 69.5 percent of all drug-involved overdose deaths.

\10\ CDC National Center for Health Statistics (NCHS), National Vital Statistics System, Mortality. NCHS Data Brief, Number 356, January 2020.

In the United States, isotonitazene has been co-identified with other substances in 18 postmortem cases, and DEA is aware of an additional death in January 2020, involving isotonitazene. These deaths associated with isotonitazene occurred in five states: Illinois (9), Indiana (7), Minnesota (1), Pennsylvania (1), and Wisconsin (1). Information gathered from case histories and autopsy findings shows that isotonitazene use is similar to that of classic opioid agonists. Evidence obtained from reported cases of death scenarios suggests that isotonitazene, similar to heroin, can be used intravenously.\11\

\11\ Krotulski AJ, Papsun DM, Kacinko SL, and Logan BK (2020). Isotonitazene Quantitation and Metabolite Discovery in Authentic Forensic Casework. Journal of Analytical Toxicology. [Epub ahead of print].

The introduction of potent synthetic opioids such as isotonitazene into the illicit market exacerbates problematic opioid use for those seeking these powerful opioids. As documented by a published toxicology report, poly-substance abuse remains common in fatalities associated with the abuse of isotonitazene.\12\

\12\ Id.

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Finding of Necessity of Schedule I Placement To Avoid Imminent Hazard to Public Safety

In accordance with **21 U.S.C. 811**(h)(3), based on the available data and information summarized above, the uncontrolled manufacture, distribution, reverse distribution, importation, exportation, conduct of research and chemical analysis, possession, and abuse of isotonitazene pose an imminent hazard to the public safety. DEA is not aware of any currently accepted medical uses for isotonitazene in the United States. A substance meeting the statutory requirements for temporary scheduling, found in 21 U.S.C. 811(h)(1), may only be placed in schedule I. 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. Available data and information for isotonitazene indicate that this substance has 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. As required by 21 U.S.C. 811(h)(4), by a letter dated March 2, 2020, the Acting Administrator notified the Assistant Secretary for Health of DEA's intention to temporarily place isotonitazene in schedule I. DEA subsequently published a Notice of Intent in the Federal Register on June 18, 2020. 85 FR 38619.

Conclusion

In accordance with the provisions of **21 U.S.C. 811**(h), the Acting Administrator considered available data and information, and herein sets forth the grounds for his determination that it is necessary to temporarily schedule N,N-diethyl-2-(2-(4 isopropoxybenzyl)-5-nitro-1H-benzimidazol-1-yl)ethan-1-amine (commonly known as: Isotonitazene) in schedule I of the CSA to avoid an imminent hazard to the public safety.

Because the Acting Administrator hereby finds it necessary to temporarily place isotonitazene in schedule I to avoid an imminent hazard to the public safety, this temporary order scheduling this substance is effective on the date of publication in the Federal Register, and will be in effect for a period of two years, with a possible extension of one additional year, pending completion of the regular (permanent) scheduling process. **21 U.S.C. 811**(h)(1) and (2).

The CSA sets forth specific criteria for scheduling a drug or other substance. Regular scheduling actions in accordance with **21 U.S.C. 811**(a) are subject to formal rulemaking procedures done "on the record after opportunity for a hearing" conducted pursuant to the provisions of 5 U.S.C. 556 and 557. 21 U.S.C. 811. The regular scheduling process of formal rulemaking affords interested parties with appropriate process and the government with any additional relevant information needed to make a determination. Final decisions that conclude the regular scheduling process of formal rulemaking are subject to judicial review. **21 U.S.C. 877.** Temporary scheduling orders are not subject to judicial review. 21 U.S.C. 811(h)(6).

Requirements for Handling

Upon the effective date of this temporary order, isotonitazene will be subject to the regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, reverse distribution, importation, exportation, engagement in research, and conduct of instructional activities or chemical analysis with, and possession of schedule I controlled substances, including the following:

1. *Registration.* Any person who handles (manufactures, distributes, reverse distributes, imports, exports, engages in research, or conducts instructional activities or chemical analysis with, or possesses), or who desires to handle, isotonitazene must be registered with DEA to conduct such activities pursuant to **21 U.S.C. 822, 823, 957,** and **958,** and in accordance with **21 CFR parts 1301** and **1312,** as of August 20, 2020. Any person who currently handles isotonitazene, and is not registered with DEA, must submit an application for registration and may not continue to handle isotonitazene as of August 20, 2020, unless DEA has approved that application for registration pursuant to 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312. Retail sales of schedule I controlled substances to the general public are not allowed under the CSA. Possession of any quantity of these substances in a manner not authorized by the CSA on or after August 20, 2020, is unlawful and those in possession of any quantity of these substances may be subject to prosecution pursuant to the CSA.

2. *Disposal of stocks.* Any person who does not desire or is not able to obtain a schedule I registration to handle isotonitazene must surrender all currently held quantities of isotonitazene.

3. *Security.* Isotonitazene is subject to schedule I security requirements and must be handled and stored pursuant to **21 U.S.C. 821, 823, 871**(b), and in accordance with **21 CFR 1301.71-1301.93,** as of August 20, 2020. Non-practitioners handling isotonitazene must also comply with the employee screening requirements of **21 CFR 1301.90-1301.93.**

4. *Labeling and Packaging.* All labels, labeling, and packaging for commercial containers of isotonitazene must be in compliance with **21 U.S.C. 825, 958**(e), and be in accordance with **21 CFR part 1302.** Current DEA registrants shall have 30 calendar days from August 20, 2020, to comply with all labeling and packaging

requirements.

5. *Inventory.* Every DEA registrant who possesses any quantity of isotonitazene on the effective date of this order must take an inventory of all stocks of these substances on hand, pursuant to **21 U.S.C. 827** and **958**, and in accordance with **21 CFR 1304.03**, **1304.04**, and **1304.11**. Current DEA registrants shall have 30 calendar days from the effective date of this order to be in compliance with all inventory requirements. After the initial inventory, every DEA registrant must take an inventory of all controlled substances (including isotonitazene) on hand on a biennial basis, pursuant to 21 U.S.C. 827 and 958, and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11.

6. *Records.* All DEA registrants must maintain records with respect to isotonitazene pursuant to **21 U.S.C. 827** and **958**, and in accordance with **21 CFR parts 1304, 1312, 1317**, and **Sec. 1307.11**. Current DEA registrants authorized to handle isotonitazene shall have 30 calendar days from the effective date of this order to be in compliance with all recordkeeping requirements.

7. *Reports.* All DEA registrants who manufacture or distribute isotonitazene must submit reports pursuant to **21 U.S.C. 827** and in accordance with **21 CFR parts 1304** and **1312** as of August 20, 2020.

8. *Order Forms.* All DEA registrants who distribute isotonitazene must comply with order form requirements pursuant to **21 U.S.C. 828** and in accordance with **21 CFR part 1305** as of August 20, 2020.

9. *Importation and Exportation.* All importation and exportation of isotonitazene must be in compliance with **21 U.S.C. 952, 953, 957, 958**, and in accordance with **21 CFR part 1312** as of August 20, 2020.

10. *Quota.* Only DEA registered manufacturers may manufacture isotonitazene in accordance with a quota assigned pursuant to **21 U.S.C. 826** and in accordance with **21 CFR part 1303** as of August 20, 2020.

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11. *Liability.* Any activity involving isotonitazene not authorized by, or in violation of the CSA, occurring as of August 20, 2020, is unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

Regulatory Matters

21 U.S.C. 811(h) provides for a temporary scheduling action where such action is necessary to avoid an imminent hazard to the public safety. As provided in this subsection, the Attorney General may, by order, schedule a substance in schedule I on a temporary basis. Such an order may not be issued before the expiration of 30 days from: (1) The publication of a notice in the Federal Register of the intention to issue such order and the grounds upon which such order is to be issued, and (2) the date that notice of the proposed temporary scheduling order is transmitted to the Assistant Secretary of HHS. 21 U.S.C. 811(h)(1).

Inasmuch as **21 U.S.C. 811(h)** directs that temporary scheduling actions be issued by order and sets forth the procedures by which such orders are to be issued, including the requirement of a publication in the Federal Register of a Notice of Intent, the notice-and-comment requirements of section 553 of the Administrative Procedure Act (APA), 5 U.S.C. 553, do not apply to this temporary scheduling order. The APA expressly differentiates between an order and a rule, as it defines an "order" to mean a "final disposition, whether affirmative, negative, injunctive, or declaratory in form, of an agency in a matter other than rule making." 5 U.S.C. 551(6) (emphasis added). The specific language chosen by Congress indicates an intention for DEA to proceed through the issuance of an order instead of proceeding by rulemaking. Given that Congress specifically requires the Attorney General to follow rulemaking procedures for other kinds of scheduling actions, see 21 U.S.C. 811(a), it is noteworthy that, in 21 U.S.C. 811(h), Congress authorized the issuance of temporary scheduling actions by order rather than by rule.

In the alternative, even assuming that this action might be subject to section 553 of the APA, the Acting Administrator finds that there is good cause to forgo the notice-and-comment requirements of section 553, as any further delays in the process for issuance of temporary scheduling orders would be impracticable and contrary to the public interest in view of the manifest urgency to avoid an imminent hazard to the public safety.

Although DEA believes this temporary scheduling order is not subject to the notice-and-comment requirements of section 553 of the APA, DEA notes that in accordance with **21 U.S.C. 811(h)(4)**, the Acting Administrator took into consideration comments submitted by the Assistant Secretary in response to the notice that DEA transmitted to the Assistant Secretary pursuant to such subsection.

Further, DEA believes that this temporary scheduling action is not a "rule" as defined by 5 U.S.C. 601(2), and, accordingly, is not subject to the requirements of the Regulatory Flexibility Act. The requirements for the preparation of an initial regulatory flexibility analysis in 5 U.S.C. 603(a) are not applicable where, as here, DEA is not required by section 553 of the APA or any other law to publish a general notice of proposed rulemaking.

In accordance with the principles of Executive Orders (E.O.) 12866 and 13563, this action is not a significant regulatory action. E.O. 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, if regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health, and safety effects; distributive impacts; and equity). E.O. 13563 is supplemental to and reaffirms the principles, structures, and definitions governing regulatory review as established in E.O. 12866. E.O. 12866 classifies a "significant regulatory action," requiring review by the Office of Management and Budget (OMB), as any regulatory action that is likely to result in a rule that may: (1) Have an annual effect on the economy of $100 million or more or adversely affect in a material way the economy; a sector of the economy; productivity; competition; jobs; the environment; public health or safety; or State, local, or tribal governments or communities; (2) create a serious inconsistency or otherwise interfere with an action taken or planned by another agency; (3) materially alter the budgetary impact of entitlements, grants, user fees, or loan programs, or the rights and obligations of recipients thereof; or (4) raise novel legal or policy issues arising out of legal mandates, the President's priorities, or the principles set forth in the E.O. Because this is not a rulemaking action, this is not a significant regulatory action as defined in Section 3(f) of E.O. 12866. In addition, because this action is not considered an E.O. 12866 "significant regulatory action," it does not meet the definition of an E.O. 13771 regulatory action. Therefore, the repeal and cost offset requirements of E.O. 13771 have not been triggered.

This action will not have substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government. Therefore, in accordance with E.O. 13132 (Federalism), it is determined that this action does not have sufficient federalism implications to warrant the preparation of a Federalism Assessment.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, DEA amends 21 CFR part 1308 as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

- 1. The authority citation for part 1308 continues to read as follows:

  Authority: 21 U.S.C. 811, 812, 871(b), 956(b), unless otherwise noted.

- 2. In **Sec. 1308.11**, add paragraph (h)(48) to read as follows:

Sec. 1308.11 Schedule I

* * * * *

(h) * * *

(48) *N,N*-diethyl-2-(2-(4 isopropoxybenzyl)-5-nitro-1*H*-benzimidazol-1-yl)ethan-1-amine, its isomers, esters, ethers, salts and salts of isomers, esters and ethers (Other names: isotonitazene; *N,N*-diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine)	9614

* * * * *

Timothy J. Shea,
Acting Administrator.

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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-477]

Schedules of Controlled Substances: Placement of Zipeprol in Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Drug Enforcement Administration (DEA) proposes placing the substance zipeprol (Chemical name: 1-methoxy-3-[4-(2-methoxy-2-phenylethyl)piperazin-1-yl]-1-phenylpropan-2-ol), including its isomers, esters, ethers, salts, and salts of isomers, esters, and ethers, whenever the existence of such isomers, esters, ethers and salts is possible, in schedule I of the Controlled Substances Act. This action is being taken to enable the United States to meet its obligations under the 1971 Convention on Psychotropic Substances. If finalized, this action would impose the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances on persons who handle (manufacture, distribute, reverse distribute, import, export, engage in research, conduct instructional activities or chemical analysis with, or possess), or propose to handle zipeprol.

DATES: Comments must be submitted electronically or postmarked on or before July 13, 2020.

Interested persons may file a request for hearing or waiver of hearing pursuant to 21 Code of Federal Regulations (CFR) **1308.44** and in accordance with **21 CFR 1316.45** and/or **1316.47**, as applicable. Requests for hearing and waivers of an opportunity for a hearing or to participate in a hearing must be received on or before June 15, 2020.

ADDRESSES: Interested persons may file written comments on this proposal in accordance with **21 CFR 1308.43**(g). Commenters should be aware that the electronic Federal Docket Management System will not accept comments after 11:59 p.m. Eastern Time on the last day of the comment period. To ensure proper handling of comments, please reference "Docket No. DEA-477" on all electronic and written correspondence, including any attachments.

- *Electronic comments:* DEA encourages that all comments be submitted electronically through the Federal eRulemaking Portal, which provides the ability to type short comments directly into the comment field on the web page or attach a file for lengthier comments. Please go to http://www.regulations.gov and follow the on-line instructions at that site for submitting comments. Upon completion of your submission you will receive a Comment Tracking Number for your comment. Please be aware that submitted comments are not instantaneously available for public view on regulations.gov. If you have received a Comment Tracking Number, your comment has been successfully submitted and there is no need to resubmit the same comment.
- *Paper comments:* Paper comments that duplicate electronic submissions are not necessary and are discouraged. Should you wish to mail a paper comment in lieu of an electronic comment, it should be sent via regular or express mail to: Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrissette Drive, Springfield, Virginia 22152.

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- *Hearing requests:* All requests for a hearing and waivers of participation must be sent to: Drug Enforcement Administration, Attn: Administrator, 8701 Morrissette Drive, Springfield, Virginia 22152. All requests for hearing and waivers of participation should also be sent to: (1) Drug Enforcement Administration, Attn: Hearing Clerk/LJ, 8701 Morrissette Drive, Springfield, Virginia 22152; and (2) Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrissette Drive, Springfield, Virginia 22152.

FOR FURTHER INFORMATION CONTACT: Scott A. Brinks, Regulatory Drafting and Policy Support Section, Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (571) 362-3261.

SUPPLEMENTARY INFORMATION:

Posting of Public Comments

Please note that all comments received in response to this docket are considered part of the public record. They will, unless reasonable cause is given, be made available by the Drug Enforcement Administration (DEA) for public inspection online at http://www.regulations.gov. Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter. The Freedom of Information Act applies to all comments received. If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want it to be made publicly available, you must include the phrase "PERSONAL IDENTIFYING INFORMATION" in the first paragraph of your comment. You must also place all of the personal identifying information you do not want made publicly available in the first paragraph of your comment and identify what information you want redacted.

If you want to submit confidential business information as part of your comment, but do not want it to be made publicly available, you must include the phrase "CONFIDENTIAL BUSINESS INFORMATION" in the first paragraph of your comment. You must also prominently identify the confidential business information to be redacted within the comment.

Comments containing personal identifying information and confidential business information identified as directed above will generally be made publicly available in redacted form. If a comment has so much confidential business information that it cannot be effectively redacted, all or part of that comment may not be made publicly available. Comments posted to http://www.regulations.gov may include any personal identifying information (such as name, address, and phone number) included in the text of your electronic submission that is not identified as directed above as confidential.

An electronic copy of this document and supplemental information to this proposed rule are available at http://www.regulations.gov for easy reference.

Request for Hearing or Waiver of Participation in Hearing

Pursuant to 21 United States Code (U.S.C.) 811(a), this action is a formal rulemaking "on the record after opportunity for a hearing." Such proceedings are conducted pursuant to the provisions of the Administrative Procedure Act, 5 U.S.C. 551-559. 21 CFR 1308.41-1308.45; 21 CFR part 1316, subpart D. Interested persons may file requests for a hearing or notices of intent to participate in a hearing in conformity with the requirements of 21 CFR 1308.44(a) or (b), and include a statement of interest in the proceeding and the objections or issues, if any, concerning which the person desires to be heard. Any interested person may file a waiver of an opportunity for a hearing or to participate in a hearing together with a written statement regarding the interested person's position on the matters of fact and law involved in any hearing as set forth in 21 CFR 1308.44(c).

All requests for hearing and waivers of participation must be sent to DEA using the address information provided above.

Legal Authority

The United States is a party to the 1971 United Nations Convention on Psychotropic Substances (1971 Convention), February 21, 1971, 32 U.S.T. 543, 1019 U.N.T.S. 175, as amended. Procedures respecting changes in drug schedules under the 1971 Convention are governed domestically by 21 U.S.C. 811(d). When the United States receives notification of a scheduling decision pursuant to Article 2 of the 1971 Convention indicating that a drug or other substance has been added or transferred to a schedule specified in the notification, the Secretary of the Department of Health and Human Services (HHS),\1\ after consultation with the Attorney General, shall first determine whether existing legal controls under subchapter I of the Controlled Substances Act (CSA) and the Federal Food, Drug, and Cosmetic Act (FDCA) meet the requirements of the schedule specified in the notification with respect to the specific drug or substance. 21 U.S.C. 811(d)(3). If such requirements are not met by existing controls and the Secretary of the HHS concurs in the scheduling decision, the Secretary shall recommend to the Attorney General that he initiate proceedings for scheduling the drug or substance under the appropriate schedule pursuant to 21 U.S.C. 811(a) and (b). 21 U.S.C. 811(d)(3)(B). Pursuant to 21 U.S.C. 811(a)(1), the Attorney General may, by rule, add to such a schedule or transfer between such schedules any drug or other substance, if he finds that such drug or other substance has a potential for abuse, and makes with respect to such drug or other substance the findings prescribed by 21 U.S.C. 812(b) for the schedule in which such drug is to be placed. The Attorney General has delegated this scheduling authority to the Administrator of the DEA (Administrator). 28 CFR 0.100.

\1\ As discussed in a memorandum of understanding entered into by the Food and Drug Administration (FDA) and the National Institute on Drug Abuse (NIDA), the FDA acts as the lead agency within HHS in carrying out the Secretary's scheduling responsibilities under the Controlled Substances Act, with the concurrence of NIDA. 50 FR 9518 (March 8, 1985). The Secretary of the HHS has delegated to the Assistant Secretary for Health of the HHS the authority to make domestic drug scheduling recommendations. 58 FR 35460 (July 1, 1993).

Background

Zipeprol, known chemically as 1-methoxy-3-[4-(2-methoxy-2-phenylethyl)piperazin-1-yl]-1-phenylpropan-2-ol, is pharmacologically an opioid drug with some hallucinogenic properties that has no approved medical use in the United States.

In June 1994 and January 1995, the Food and Drug Administration (FDA), on behalf of the Secretary of the HHS, published notices in the Federal Register regarding zipeprol to comply with 21 U.S.C. 811(d)(2). The 1994 notice requested information to be considered by the World Health Organization (WHO) in preparing its scientific and medical evaluation for zipeprol.\2\ The 1995 notice solicited public comment regarding a recommendation by the WHO to impose international controls on zipeprol.\3\ In

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March 1995, the United Nations Commission on Narcotic Drugs (CND), on the advice of the Director-General of the WHO, placed zipeprol in Schedule II of the 1971 Convention.\4\

\2\ FDA notice, International Drug Scheduling; Convention on Psychotropic Substances; Certain Stimulant/Hallucinogenic Drugs and Certain Nonbarbiturate Sedative Drugs, 59 FR 31639 (June 20, 1994).

\3\ FDA notice, International Drug Scheduling; Convention on Psychotropic Substances; World Health Organization Scheduling Recommendations for Seven Drug Substances, 60 FR 4169, 4173 (January 20, 1995).

\4\ United Nations Office on Drugs and Crime, CND. Decision 2 (XXXVIII). Inclusion of zipeprol in Schedule II of the Convention on Psychotropic Substances of 1971. https://www.unodc.org/pdf/decisions/decision2_38.pdf (last retrieved October 3, 2018).

As a party to the 1971 Convention, the United States is taking action to place appropriate controls on zipeprol by scheduling it under the CSA after determining that no existing legal controls under subchapter I of the CSA and the FDCA meet the requirements of the scheduling decision with respect to zipeprol. 21 U.S.C. 811(d)(3). Specifically, DEA is proposing to place zipeprol in schedule I of the CSA. Placing zipeprol in schedule I of the CSA would satisfy the United States' international obligations as set forth in Article 2, paragraph 7(b) of the 1971 Convention, and as implemented by the CSA. 21 U.S.C. 811(d)(3).

Article 2, paragraph 7(b), of the 1971 Convention sets forth the minimum requirements that the United States must meet when a substance has been added to Schedule II of the 1971 Convention. Pursuant to the 1971 Convention, the United States must require licenses for the manufacture, export and import, and distribution of zipeprol. This license requirement is accomplished by the CSA's registration requirement as set forth in 21 U.S.C. 822, 823, 957, 958, and in accordance with 21 CFR parts 1301 and 1312. In addition, the United States must adhere to specific export and import provisions set forth in the 1971 Convention. This requirement is accomplished by the CSA's export and import provisions established in 21 U.S.C. 952, 953, 957, 958, and in accordance with 21 CFR part 1312. Likewise, under Article 13, paragraphs 1 and 2, of the 1971 Convention, a party to the 1971 Convention may notify another party, through the Secretary-General of the United Nations, that it prohibits the importation of a substance in Schedule II, III, or IV of the Convention. If such notice is presented to the United States, the United States shall take measures to ensure that the named substance is not exported to the notifying country. This requirement is also accomplished by the CSA's export provisions mentioned above. Under Article 16, paragraph 4, of the 1971 Convention, the United States is required to provide annual statistical reports to the International Narcotics Control Board (INCB). Using INCB Form P, the United States shall provide the following information: (1) In regard to each substance in Schedule I and II of the 1971 Convention, quantities manufactured, exported to and imported from each country or region as well as stocks held by manufacturers; (2) in regard to each substance in Schedule II and III of the 1971 Convention, quantities used in the manufacture of exempt preparations; and (3) in regard to each substance in Schedule II--IV of the 1971 Convention, quantities used for the manufacture of non-psychotropic substances or products. Lastly, under Article 2 of the 1971 Convention, the United States must adopt measures in accordance with Article 22 to address violations of any statutes or regulations that are adopted pursuant to its obligations under the 1971 Convention. The United States complies with this provision as persons acting outside the legal framework established by the CSA are subject to administrative, civil, and/or criminal action.

Proposed Determination To Schedule Zipeprol

Pursuant to 21 U.S.C. 811(b), DEA gathered the necessary data on zipeprol and on April 3, 2009, submitted it to the Assistant Secretary for Health of the HHS with a request for a scientific and medical evaluation of available information and a scheduling recommendation for zipeprol. On May 20, 2013, HHS provided to DEA a written scientific and medical evaluation and scheduling recommendation entitled, "Basis for the Recommendation for Control of Zipeprol and Its Salts in Schedule I of the Controlled Substances Act." Pursuant to 21 U.S.C. 811(b), this document contained HHS' eight-factor analysis of zipeprol, along with its recommendation that zipeprol be placed in schedule I of the CSA.

In response, DEA reviewed the scientific and medical evaluation and scheduling recommendation provided by the HHS and all other relevant data, and completed its own eight-factor review document pursuant to 21 U.S.C. 811(c). Since receiving the HHS recommendation, no additional studies have been published in the scientific literature. Included below is a brief summary of each factor as analyzed by HHS and DEA in their respective eight-factor analyses, and as considered by DEA in its proposed scheduling determination. Please note that both DEA and HHS analyses are available in their entirety under "Supporting Documents" of the public docket for this proposed rule at http://www.regulations.gov under docket number "DEA-477."

1. *The Drug's Actual or Relative Potential for Abuse:* As reported by HHS, there are numerous reports indicating that abuse of zipeprol resulted in seizures, comas, amnesia, hallucinations, and death in countries where zipeprol has been marketed as an antitussive. The pharmacological effects of zipeprol are similar to opioids in schedule II of the CSA such as morphine; however, zipeprol is a weak opioid relative to morphine. Hallucinations, convulsions, and opioid-like tolerance and dependence are observed in humans following zipeprol intake. Zipeprol abuse is associated with psychological and physical dependence. Abuse liability studies suggest that the primary motivation for zipeprol abuse was reaching the opioid-like, hypnotic sedative effects and euphoria associated with this drug.

2. *Scientific Evidence of the Drug's Pharmacological Effects, if Known:* Zipeprol binds with low to moderate affinity to mu and kappa opioid receptors, has a moderate affinity for sigma 1 receptors, and has a strong affinity for sigma 2 receptors. Animal testing data in monkeys, rats and mice show that zipeprol is self-administered. Acute cardiovascular and respiratory toxicity was observed in animals continuously infused with zipeprol. Published clinical reports have indicated that euphoric effects are observed at doses ranging from 3- to 10- fold higher than the therapeutic daily dose range (75-150 mg/day). Generalized seizures were reported at relatively low doses (375 mg) but still higher than the therapeutic dose range.

3. *The State of Current Scientific Knowledge Regarding the Drug or Other Substance:* Zipeprol, also known as 1-methoxy-3-[4-(2-methoxy-2-phenylethyl) piperazin-1-yl]-1-phenylpropan-2-ol, has a molecular weight of 322.37 g/mol. Zipeprol is extensively metabolized in humans into four major metabolites. Zipeprol is not expected to be detected in urine with a normal pH. When urine pH rises above 6.2, unchanged zipeprol is reabsorbed whereas under acidic urine conditions (pH < 5.0), approximately 1-5 percent of zipeprol is excreted unchanged. There is no currently accepted medical use of zipeprol in the United States. In other countries, zipeprol was used as a cough suppressant (antitussive), but there is no longer any reported manufacture of, consumption of, stocks or trade of zipeprol.

4. *Its History and Current Pattern of Abuse:* There have been numerous

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reports of zipeprol abuse from Brazil, Chile, France, Italy, Mexico, the Republic of Korea, Switzerland, and the former Yugoslavia during the 1980s and 1990s. These reports suggest the sedative, hallucinogenic, and euphorigenic effects of zipeprol, and its ability to suppress some signs of opioid withdrawal at high doses, may be the reasons for its abuse. It is important to note that the ability of one opioid to suppress withdrawal from a different opioid does not represent a beneficial effect. Ease of obtaining zipeprol by over-the-counter access may have contributed to its widespread abuse in some countries. Following these reports, many countries in Asia, Europe, and South America discontinued medical use of zipeprol. Incidences of zipeprol abuse were not reported after placement of zipeprol in Schedule II of the 1971 Convention on Psychotropic Substances in 1995 (CND Dec. 38/2). Queries of DEA's System to Retrieve Information from Drug Evidence (STRIDE)/STARLIMS \5\ and the National Forensic Laboratory Information System (NFLIS) \6\ databases on October 3, 2018, did not generate any reports of zipeprol, suggesting that it is not trafficked in the United States.

\5\ STRIDE is a database of drug exhibits sent to DEA laboratories for analysis. Exhibits from the database are from DEA, other federal agencies, and law enforcement agencies. On October 1, 2014, STARLIMS replaced STRIDE as DEA laboratory drug evidence data system of record.

\6\ NFLIS is a national drug forensic laboratory reporting system that systematically collects results from drug chemistry analyses conducted by state and local forensic laboratories across the country. The NFLIS participation rate, defined as the percentage of the national drug caseload represented by laboratories that have joined NFLIS, is over 97 percent. NFLIS includes drug chemistry results from completed analyses only.

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5. *The Scope, Duration, and Significance of Abuse:* The lack of abuse and overdose associated with zipeprol is most likely due to its lack of availability for medical use in the United States.

6. *What, if any, Risk There is to the Public Health:* Currently in the United States, zipeprol is not an FDA-approved drug, and there have been no reports or epidemiological studies submitted to FDA regarding its abuse. In countries where it was available for medical use, zipeprol became a significant health problem. Based on the available clinical data, zipeprol has the same risks to public health as schedule I or schedule II substances. Such risks include deaths due to voluntary or accidental acute intoxications and the potential for psychological and physical dependence.

7. *Its Psychic or Physiological Dependence Liability:* Psychological and physiological dependence is associated with zipeprol. Several clinical studies examined and described physical dependence and withdrawal effects associated with zipeprol abuse. Main signs of zipeprol withdrawal include sweating, diarrhea, anxiety, insomnia, dyspnea, yawning, and pain. The euphoric and hallucinogenic effects associated with zipeprol and other opioid-like drugs serve as reinforcers and can result in psychological dependence and are supported by case studies with zipeprol abusers.

8. *Whether the Substance is an Immediate Precursor of a Substance Already Controlled Under the CSA:* DEA and HHS find that zipeprol is not an immediate precursor of a substance already controlled under the CSA.

Conclusion: Based on consideration of the scientific and medical evaluation and accompanying recommendation of HHS, and based on DEA's consideration of its own eight-factor analysis, DEA finds that these facts and all relevant data constitute substantial evidence of potential for abuse of zipeprol. As such, DEA hereby proposes to schedule zipeprol as a controlled substance under the CSA.

Proposed Determination of Appropriate Schedule

The CSA establishes five schedules of controlled substances known as schedules I, II, III, IV, and V. The CSA also outlines the findings required to place a drug or other substance in any particular schedule. **21 U.S.C. 812(b)**. After consideration of the analysis and recommendation of the Assistant Secretary for Health of the HHS and review of all available data, the Acting Administrator of the DEA (Acting Administrator), pursuant to 21 U.S.C. 812(b)(1), finds that:

(1) Zipeprol has a high potential for abuse. Widespread reports of zipeprol abuse have occurred in countries that have marketed zipeprol. Zipeprol is self-administered in animals and clinical studies reported that zipeprol abuse is related to its opioid, sedative, hallucinogenic, and euphorigenic effects. Epidemiological reports on zipeprol, worldwide, have indicated that adverse reactions (primarily seizures) are caused by zipeprol abuse and dependence.

(2) There are no approved New Drug Applications for zipeprol and no known therapeutic applications for zipeprol in the United States.\7\ Therefore, zipeprol has no currently accepted medical use in treatment in the United States.

\7\ Although there is no evidence suggesting that zipeprol has a currently accepted medical use in treatment in the United States, it bears noting that a drug cannot be found to have such medical use unless DEA concludes that it satisfies a five-part test. Specifically, with respect to a drug that has not been approved by the FDA, to have a currently accepted medical use in treatment in the United States, all of the following must be demonstrated:

i. the drug's chemistry must be known and reproducible; ii. there must be adequate safety studies;

iii. there must be adequate and well-controlled studies proving efficacy;

iv. the drug must be accepted by qualified experts; and

v. the scientific evidence must be widely available.

57 FR 10499 (1992).

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(3) There is a lack of accepted safety for use of zipeprol under medical supervision. Zipeprol was first approved and introduced as an antitussive in France and Italy during the late 1970s. Following several reports of abuse and overdosing from zipeprol, this drug was withdrawn in the early to mid-1990s.

Based on these findings, the Acting Administrator concludes that zipeprol warrants control in schedule I of the CSA. **21 U.S.C. 812**(b)(1). More precisely, because of its opioid effects, and producing opioid-like tolerance and dependence in humans, DEA is proposing to place zipeprol in **21 CFR 1308.11**(b) (the opiates category of schedule I). As such, the proposed control of zipeprol includes the substance as well as its isomers, esters, ethers, salts, and salts of isomers, esters and ethers, whenever the existence of such isomers, esters, ethers and salts is possible within the specific chemical designation.

Requirements for Handling Zipeprol

If this rule is finalized as proposed, zipeprol would be subject to the CSA's schedule I regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, reverse distribution, import, export, engagement in research, conduct of instructional activities or chemical analysis with, and possession of schedule I controlled substances, including the following:

1. *Registration.* Any person who handles (manufactures, distributes, reverse distributes, imports, exports, engages in research, or conducts instructional activities or chemical analysis with, or possesses) zipeprol, or who desires to handle zipeprol, would need to be registered with DEA to conduct such activities pursuant to **21 U.S.C. 822, 823, 957, 958**, and in accordance with **21 CFR parts 1301** and **1312** as of the effective date of a final scheduling action. Any person who currently handles zipeprol, and is not registered with DEA, would need to submit an application for registration

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and may not continue to handle zipeprol after the effective date of a final scheduling action unless DEA has approved that application for registration pursuant to **21 U.S.C. 822, 823, 957, 958**, and in accordance with **21 CFR parts 1301** and **1312.**

2. *Disposal of stocks.* Any person who does not desire or is not able to obtain a schedule I registration would be required to surrender all quantities of currently held zipeprol, or transfer all quantities of currently held zipeprol to a person registered with DEA before the effective date of a final scheduling action in accordance with all applicable federal, state, local, and tribal laws. As of the effective date of a final scheduling action, zipeprol would be required to be disposed of in accordance with **21 CFR part 1317**, in addition to all other applicable federal, state, local, and tribal laws.

3. *Security.* Zipeprol would be subject to schedule I security requirements and would need to be handled and stored pursuant to **21 U.S.C. 821** and **823**, and in accordance with **21 CFR 1301.71-1301.93** as of the effective date of a final scheduling action.

4. *Labeling and Packaging.* All labels, labeling, and packaging for commercial containers of zipeprol would need to be in compliance with **21 U.S.C. 825** and **958**(e), and be in accordance with **21 CFR part 1302** as of the effective date of a final scheduling action.

5. *Quota.* Only registered manufacturers would be permitted to manufacture zipeprol in accordance with a quota assigned pursuant to **21 U.S.C. 826** and in accordance with **21 CFR part 1303** as of the effective date of a final scheduling action.

6. *Inventory.* Every DEA registrant who possesses any quantity of zipeprol on the effective date of a final scheduling action would be required to take an inventory of zipeprol on hand at that time, pursuant to **21 U.S.C. 827** and **958**, and in accordance with **21 CFR 1304.03, 1304.04**, and **1304.11**(a) and (d).

Any person who becomes registered with DEA on or after the effective date of the final scheduling action would be required to take an initial inventory of all stocks of controlled substances (including zipeprol) on hand on the date the registrant first engages in the handling of controlled substances, pursuant to **21 U.S.C. 827** and **958**, and in accordance with **21 CFR 1304.03, 1304.04**, and **1304.11**(a) and (b).

After the initial inventory, every DEA registrant would be required to take an inventory of all controlled substances (including zipeprol) on hand every two years, pursuant to **21 U.S.C. 827** and **958**, and in accordance with **21 CFR 1304.03, 1304.04**, and **1304.11.**

7. *Records and Reports.* Every DEA registrant would be required to maintain records and submit reports pursuant to **21 U.S.C. 827** and **958**, and in accordance with **21 CFR parts 1304, 1312**, and **1317** as of the effective date of a final scheduling action. Manufacturers and distributors would be required to submit reports regarding zipeprol to the Automation of Reports and Consolidated Order System pursuant to 21 U.S.C. 827 and in accordance with 21 CFR parts 1304 and 1312 as of the effective date of a final scheduling action.

8. *Order Forms.* Every DEA registrant who distributes zipeprol would be required to comply with order form requirements, pursuant to **21 U.S.C. 828**, and in accordance with **21 CFR part 1305** as of the effective date of a final scheduling action.

9. *Importation and Exportation.* All importation and exportation of zipeprol would need to be in compliance with **21 U.S.C. 952, 953, 957**, and **958**, and in accordance with **21 CFR part 1312** as of the effective date of a final scheduling action.

10. *Liability.* Any activity involving zipeprol not authorized by, or in violation of, the CSA or its implementing regulations, would be unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

Regulatory Analyses

Executive Orders 12866, 13563, and 13771, Regulatory Planning and Review, Improving Regulation and Regulatory Review, and Reducing Regulation and Controlling Regulatory Costs

In accordance with **21 U.S.C. 811**(a), this proposed scheduling action is subject to formal rulemaking procedures performed "on the record after opportunity for a hearing," which are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth the procedures and criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget (OMB) pursuant to section 3(d)(1) of Executive Order 12866 and the principles reaffirmed in Executive Order 13563.

This rulemaking is not an Executive Order 13771 regulatory action because this rule is not significant under Executive Order 12866.

Executive Order 12988, Civil Justice Reform

This proposed regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of Executive Order 12988, Civil Justice Reform, to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132, Federalism

This proposed rulemaking does not have federalism implications warranting the application of Executive Order 13132. The proposed rule does not have substantial direct effects on the States, on the relationship between the national government and the States, or the distribution of power and responsibilities among the various levels of government.

Executive Order 13175, Consultation and Coordination With Indian Tribal Governments

This proposed rule does not have tribal implications warranting the application of Executive Order 13175. It does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal Government and Indian tribes, or on the distribution of power and responsibilities between the Federal Government and Indian tribes.

Paperwork Reduction Act of 1995

This action does not impose a new collection of information requirement under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521).

Regulatory Flexibility Act

The Acting Administrator, in accordance with the Regulatory Flexibility Act (RFA), 5 U.S.C. 601-602, has reviewed this proposed rule, and by approving it, certifies that it will not have a significant economic impact on a substantial number of small entities.

DEA proposes placing the substance zipeprol (chemical name: 1-methoxy-3-[4-(2-methoxy-2-phenylethyl)piperazin-1-yl]-1-phenylpropan-2-ol), including its isomers, esters, ethers, salts, and salts of isomers, esters, and ethers, whenever the existence of such isomers, esters, ethers and salts is possible, in schedule I of the CSA. This action is being taken to enable the United States to meet its obligations under the 1971 Convention on Psychotropic Substances. If finalized, this action would impose the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances on persons who handle (manufacture, distribute, reverse distribute, import, export, engage in research, conduct instructional activities or chemical

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analysis with, or possess), or propose to handle zipeprol.

According to HHS, zipeprol has a high potential for abuse, has no currently accepted medical use in treatment in the United States, and lacks accepted safety for use under medical supervision. DEA's research confirms that there is no commercial market for zipeprol in the United States. Additionally, queries of DEA's STRIDE/STARLIMS and the NFLIS databases on October 3, 2018, did not generate any reports of zipeprol, suggesting that it is not trafficked in the United States. Therefore, DEA estimates that no United States entity currently handles zipeprol and does not expect any United States entity to handle zipeprol in the foreseeable future. DEA concludes that no United States entity would be affected by this rule if finalized. As such, the proposed rule will not have a significant effect on a substantial number of small entities.

Unfunded Mandates Reform Act of 1995

On the basis of information contained in the "Regulatory Flexibility Act" section above, DEA has determined and certifies pursuant to the Unfunded Mandates Reform Act (UMRA) of 1995 (2 U.S.C. 1501 et seq.), that this action would not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any 1 year * * *." Therefore, neither a Small Government Agency Plan nor any other action is required under provisions of the UMRA of 1995.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, 21 CFR part 1308 is proposed to be amended to read as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

- 1. The authority citation for 21 CFR part 1308 continues to read as follows:

  Authority: 21 U.S.C. 811, 812, 871(b), **956**(b), unless otherwise noted.

- 2. In **Sec. 1308.11**, add paragraph (b)(71) to read as follows:

Sec. 1308.11 Schedule I.

* * * * *

(b) * * *

(71) Zipeprol	9873

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Uttam Dhillon,
Acting Administrator.

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Rules - 2019

[Federal Register Volume 84, Number 207 (Friday, October 25, 2019)]
[Rules and Regulations]
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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-507]

Schedules of Controlled Substances: Placement of Cyclopropyl Fentanyl, Methoxyacetyl fentanyl, ortho-Fluorofentanyl, and para-Fluorobutyryl Fentanyl in Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final amendment; final order.

SUMMARY: With the issuance of this final order, the Acting Administrator of the Drug Enforcement Administration

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maintains the placement of the substances cyclopropyl fentanyl (N-(1-phenethylpiperidin-4-yl)-N-phenylcyclopropanecarboxamide), methoxyacetyl fentanyl (2-methoxy-N-(1-phenethylpiperidin-4-yl)-N-phenylacetamide), ortho-fluorofentanyl (N-(2-fluorophenyl)-N-(1-phenethylpiperidin-4-yl)propionamide), and para-fluorobutyryl fentanyl (N-(4-fluorophenyl)-N-(1-phenethylpiperidin-4-yl)butyramide), including their isomers, esters, ethers, salts, and salts of isomers, esters and ethers, in schedule I of the Controlled Substances Act. This scheduling action discharges the United States' obligations under the Single Convention on Narcotic Drugs (1961). This action continues to impose the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances on persons who handle (manufacture, distribute, import, export, engage in research or conduct instructional activities with, or possess), or propose to handle, cyclopropyl fentanyl, methoxyacetyl fentanyl, ortho-fluorofentanyl, and para-fluorobutyryl fentanyl.

DATES: Effective October 25, 2019.

FOR FURTHER INFORMATION CONTACT: Scott A. Brinks, Regulatory Drafting and Policy Support Section, Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (202) 598-6812.

SUPPLEMENTARY INFORMATION:

Legal Authority

Section 201(d)(1) of the Controlled Substances Act (CSA) (**21 U.S.C. 811**(d)(1)) states that, if control of a substance is required "by United States obligations under international treaties, conventions, or protocols in effect on October 27, 1970, the Attorney General shall issue an order controlling such drug under the schedule he deems most appropriate to carry out such obligations, without regard to the findings required by [section 201(a) (21 U.S.C. 811(a)] or section [202(b) (**21 U.S.C. 812**(b)) of the Act] and without regard to the procedures prescribed by [section 201 (a) and (b) (21 U.S.C. 811(a) and (b)]." If a substance is added to one of the schedules of the Single Convention on Narcotic Drugs (1961), then, in accordance with article 3, paragraph 7 of the Convention, as a signatory Member State, the United States is obligated to control the substance under its national drug control legislation, the CSA. The Attorney General has delegated scheduling authority under 21 U.S.C. 811 to the Administrator of the Drug Enforcement Administration (DEA). 28 CFR 0.100.

Background

On May 23, 2019, the Secretary-General of the United Nations send a letter to the Secretary of State of the United States advising him that during the 62nd session of the Commission on Narcotic Drugs, cyclopropyl fentanyl, methoxyacetyl fentanyl, ortho-fluorofentanyl, and para-fluorobutyryl fentanyl were added to Schedule I of the Single Convention on Narcotic Drugs (1961). This letter was prompted by a decision at the 62nd session of the Commission on Narcotic Drugs in March 2019 to schedule cyclopropyl fentanyl, methoxyacetyl fentanyl, ortho-fluorofentanyl, and para-fluorobutyryl fentanyl under Schedule I of the Single Convention on Narcotic Drugs. As a signatory Member State to the Single Convention on Narcotic Drugs, the United States is obligated to control cyclopropyl fentanyl, methoxyacetyl fentanyl, ortho-fluorofentanyl, and para-fluorobutyryl fentanyl under its national drug control legislation, the CSA, in the schedule deemed most appropriate to carry out its international obligations. **21 U.S.C. 811**(d)(1).

Cyclopropyl Fentanyl, Methoxyacetyl Fentanyl, ortho-Fluorofentanyl, and para-Fluorobutyryl Fentanyl

Cyclopropyl fentanyl (83 FR 469, January 4, 2018), methoxyacetyl fentanyl and ortho-fluorofentanyl (82 FR 49504, October 26, 2017), and para-fluorobutyryl fentanyl (83 FR 4580, February 1, 2018) were temporarily controlled in schedule I of the CSA upon finding that they pose an imminent hazard to the public safety. These substances share pharmacological profiles similar to morphine, fentanyl, and other synthetic opioids which act as [micro]-opioid receptor agonists. For this reason, cyclopropyl fentanyl, methoxyacetyl fentanyl, ortho-fluorofentanyl, and para-fluorobutyryl fentanyl are abused for their opioid-like effects. Law enforcement and public health reports demonstrate the illicit use and distribution of these substances, which are similar to that of heroin and prescription opioid analgesics.

Cyclopropyl fentanyl, methoxyacetyl fentanyl, ortho-fluorofentanyl, and para-fluorobutyryl fentanyl were identified in law enforcement encounters in the United States. The National Forensic Laboratory Information System (NFLIS) is a national drug forensic laboratory reporting system that systematically collects results from drug chemistry analyses conducted by other federal, state and local forensic laboratories across the country. According to NFLIS,\1\ cyclopropyl fentanyl (first reported in 2016) was identified in 2,461 exhibits submitted to forensic laboratories, methoxyacetyl fentanyl (first reported in 2017) was identified in 1,718 exhibits, ortho-fluorofentanyl (first reported in 2016) was identified in 13 exhibits, and para-fluorobutyryl fentanyl (first reported in 2015) was identified in 309 exhibits.

\1\ NFLIS was queried on June 7, 2019. Data are still being collected for January 2019--June 2019 due to the normal lag period for labs reporting to NFLIS.

The DEA is not aware of any claims or any medical or scientific literature suggesting that cyclopropyl fentanyl, methoxyacetyl fentanyl, ortho-fluorofentanyl, or para-fluorobutyryl fentanyl have a currently accepted medical use in treatment in the United States. In addition, the Department of Health and Human Services (HHS)

advised the DEA, by letters dated September 6, 2017 (cyclopropyl fentanyl), July 14, 2017 (methoxyacetyl fentanyl), June 9, 2017 (ortho-fluorofentanyl), and November 8, 2017 (para-fluorobutyryl fentanyl) that there were no investigational new drug applications or approved new drug applications for these substances.

The DEA requested that HHS conduct a scientific and medical evaluation and a scheduling recommendation for methoxyacetyl fentanyl and ortho-fluorofentanyl (by letter dated April 18, 2018) and cyclopropyl fentanyl and para-fluorobutyryl fentanyl (by letter dated November 5, 2018). Regardless of these requests and any potential responses from HHS, the DEA is not required under **21 U.S.C. 811**(d)(1) to make any findings otherwise required by 21 U.S.C. 811(a) or **812**(b), and is not required to follow the procedures prescribed by 21 U.S.C. 811(a) and (b). The Acting Administrator advised HHS, by letter dated September 6, 2019, that the DEA no longer requires scientific and medical evaluations and scheduling recommendations for cyclopropyl fentanyl, methoxyacetyl fentanyl, ortho-fluorofentanyl, and para-fluorobutyryl fentanyl. These evaluations are no longer required due to the placement of these substances in Schedule I of the Single Convention on Narcotic Drugs (1961) in March 2019. Therefore, consistent with the framework of 21 U.S.C. 811(d), the DEA concludes that cyclopropyl fentanyl, methoxyacetyl fentanyl, ortho-fluorofentanyl, and para-fluorobutyryl fentanyl have no currently accepted medical use in treatment in the United States and are most

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appropriately placed in schedule I of the CSA, the same schedule in which they currently reside. Further, while the DEA temporarily scheduled these substances under **21 CFR 1308.11**(h), a paragraph reserved for the temporary listing of substances subject to emergency scheduling, this order moves these substances to 21 CFR 1308.11(b). As explained above, because control is required under the Single Convention on Narcotic Drugs (1961), the DEA will not be initiating regular rulemaking proceedings to schedule these substances pursuant to **21 U.S.C. 811**(a).

Conclusion

In order to meet the United States' obligations under the Single Convention on Narcotic Drugs (1961) and because cyclopropyl fentanyl, methoxyacetyl fentanyl, ortho-fluorofentanyl, and para-fluorobutyryl fentanyl have no currently accepted medical use in treatment in the United States, the Acting Administrator of the DEA has determined that these substances should remain in schedule I of the CSA.

Requirements for Handling

Cyclopropyl fentanyl, methoxyacetyl fentanyl, ortho-fluorofentanyl, and para-fluorobutyryl fentanyl have been controlled as schedule I controlled substances since January 4, 2018, October 26, 2017, October 26, 2017, and February 1, 2018, respectively. With publication of the final order contained in this document, cyclopropyl fentanyl, methoxyacetyl fentanyl, ortho-fluorofentanyl, and para-fluorobutyryl fentanyl remain subject to the CSA's schedule I regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, importation, exportation, engagement in research, conduct of instructional activities, and possession of schedule I controlled substances, including the following:

1. *Registration.* Any person who handles (manufactures, distributes, imports, exports, engages in research or conducts instructional activities with, or possesses), or who desires to handle, cyclopropyl fentanyl, methoxyacetyl fentanyl, ortho-fluorofentanyl, and para-fluorobutyryl fentanyl must be registered with the DEA to conduct such activities pursuant to **21 U.S.C. 822, 823, 957,** and **958** and in accordance with **21 CFR parts 1301** and **1312.**

2. *Disposal of stocks.* Cyclopropyl fentanyl, methoxyacetyl fentanyl, ortho-fluorofentanyl, and para-fluorobutyryl fentanyl must be disposed of in accordance with **21 CFR part 1317**, in addition to all other applicable federal, state, local, and tribal laws.

3. *Security.* Cyclopropyl fentanyl, methoxyacetyl fentanyl, ortho-fluorofentanyl, and para-fluorobutyryl fentanyl are subject to schedule I security requirements and must be handled and stored in accordance with **21 CFR 1301.71-1301.93.**

4. *Labeling and packaging.* All labels, labeling, and packaging for commercial containers of cyclopropyl fentanyl, methoxyacetyl fentanyl, ortho-fluorofentanyl, and para-fluorobutyryl fentanyl must be in compliance with **21 U.S.C. 825** and **958**(e), and must be in accordance with **21 CFR part 1302.**

5. *Quota.* A quota assigned pursuant to **21 U.S.C. 826** and in accordance with **21 CFR part 1303** is required in order to manufacture cyclopropyl fentanyl, methoxyacetyl fentanyl, ortho-fluorofentanyl, and para-fluorobutyryl fentanyl.

6. *Inventory.* Every DEA registrant who possesses any quantity of cyclopropyl fentanyl, methoxyacetyl fentanyl, ortho-fluorofentanyl, and para-fluorobutyryl fentanyl was required to keep an inventory of all stocks of these substances on hand as of January 4, 2018, October 26, 2017, October 26, 2017, and February 1, 2018, respectively, pursuant to **21 U.S.C. 827** and **958**(e), and in accordance with **21 CFR 1304.03, 1304.04,** and **1304.11.**

7. *Records and Reports.* DEA registrants must maintain records and submit reports with respect to cyclopropyl fentanyl, methoxyacetyl fentanyl, ortho-fluorofentanyl, and para-fluorobutyryl fentanyl pursuant to **21 U.S.C. 827** and **958**(e), and in accordance with **21 CFR parts 1304, 1312,** and **1317.**

8. *Order Forms.* All DEA registrants who distribute cyclopropyl fentanyl, methoxyacetyl fentanyl, ortho-fluorofentanyl, and para-fluorobutyryl fentanyl must comply with order form requirements pursuant to **21 U.S.C. 828** and in accordance with **21 CFR part 1305.**

9. *Importation and Exportation.* All importation and exportation of cyclopropyl fentanyl, methoxyacetyl fentanyl, ortho-fluorofentanyl, and para-fluorobutyryl fentanyl must be in compliance with **21 U.S.C. 952, 953, 957,** and **958,** and in accordance with **21 CFR part 1312.**

10. *Liability.* Any activity involving cyclopropyl fentanyl, methoxyacetyl fentanyl, ortho-fluorofentanyl, and para-fluorobutyryl fentanyl not authorized by, or in violation of the CSA, is unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

Regulatory Analyses

Executive Order 12866, 13563, and 13771, Regulatory Planning and Review, Improving Regulation and Regulatory Review, and Reducing Regulation and Controlling Regulatory Costs

This action is not a significant regulatory action as defined by Executive Order 12866 (Regulatory Planning and Review), section 3(f), and the principles reaffirmed in Executive Order 13563 (Improving Regulation and Regulatory Review), and, accordingly, this action has not been reviewed by the Office of Management and Budget (OMB).

This order is not an Executive Order 13771 regulatory action.

Executive Order 12988, Civil Justice Reform

This action meets the applicable standards set forth in sections 3(a) and 3(b)(2) of Executive Order 12988 to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132, Federalism

This action does not have federalism implications warranting the application of Executive Order 13132. This action does not have substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government.

Executive Order 13175, Consultation and Coordination With Indian Tribal Governments

This action does not have tribal implications warranting the application of Executive Order 13175. The action does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal government and Indian tribes, or on the distribution of power and responsibilities between the Federal government and Indian tribes.

Administrative Procedure Act

The CSA provides for an expedited scheduling action where control is required by the United States obligations under international treaties, conventions, or protocols. **21 U.S.C. 811**(d)(1). If control is required pursuant to such international treaty, convention, or protocol, the Attorney General must issue an order controlling such drug under the schedule he deems most appropriate to carry out such obligations, without regard to the findings or procedures otherwise required for scheduling actions. Id.

To the extent that **21 U.S.C. 811**(d)(1) directs that if control is required by the United States' obligations under international treaties, conventions, or protocols in effect on October 27, 1970, scheduling actions shall be issued by order (as compared to scheduling pursuant to 21 U.S.C. 811(a) by rule), the DEA believes that the notice and comment requirements of section 553 of the Administrative Procedure Act (APA), 5 U.S.C. 553, do not apply to this scheduling action. In the alternative, even if this action does constitute "rule making" under 5 U.S.C. 551(5), this

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action is exempt from the notice and comment requirements of 5 U.S.C. 553 pursuant to 21 U.S.C. 553(a)(1) as an action involving a foreign affairs function of the United States given that this action is being done in accordance with **21 U.S.C. 811**(d)(1)'s requirement that the United States comply with its obligations under the specified international agreements.

Regulatory Flexibility Act

The Regulatory Flexibility Act (RFA) (5 U.S.C. 601-612) applies to rules that are subject to notice and comment under section 553(b) of the APA or any other law. As explained above, the CSA exempts this final order from notice and comment. Consequently, the RFA does not apply to this action.

Paperwork Reduction Act of 1995

This action does not impose a new collection of information requirement under the Paperwork Reduction Act of 1995. 44 U.S.C. 3501-3521. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Congressional Review Act

This action is not a major rule as defined by the Congressional Review Act (CRA), 5 U.S.C. 804. This order will not result in: "an annual effect on the economy of $100,000,000 or more; a major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; or significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based enterprises to compete with foreign based enterprises in domestic and export markets." However, pursuant to the CRA, the DEA has submitted a copy of this final order to both Houses of Congress and to the Comptroller General.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, the DEA amends 21 CFR part 1308 as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

- 1. The authority citation for part 1308 continues to read as follows:

  Authority: 21 U.S.C. 811, 812, 871(b), **956**(b), unless otherwise noted.

- 2. In **Sec. 1308.11**:
- a. Redesignate paragraphs (b)(51) through (b)(66) as (b)(55) through (70);
- b. Redesignate paragraphs (b)(41) through (b)(50) as (b)(43) through (52);
- c. Redesignate paragraphs (b)(22) through (40) as (b)(23) through (41);
- d. Add new paragraphs (b)(22), (42), (53), and (54); and
- e. Remove and reserve paragraphs (h)(19), (21), (22), and (24).

The additions read as follows:

Sec. 1308.11 Schedule I.

* * * * *

(b) * * *

(22) Cyclopropyl fentanyl (*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylcyclopropanecarboxamide)	9845

* * * * *

(42) Methoxyacetyl fentanyl (2-methoxy-*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacetamide)	9825

* * * * *

(53) *ortho*-Fluorofentanyl (*N*-(2-fluorophenyl)-*N*-(1-phenethylpiperidin-4-yl)propionamide); other name: 2-fluorofentanyl)	9816
(54) *para*-Fluorobutyryl fentanyl (*N*-(4-fluorophenyl)-*N*-(1-phenethylpiperidin-4-yl)butyramide)	9823

* * * * *

Dated: October 19, 2019.

Uttam Dhillon,
Acting Administrator.

[FR Doc. 2019-23348 Filed 10-24-19; 8:45 am]

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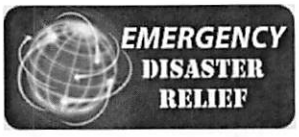

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DIVERSION CONTROL DIVISION

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Rules - 2019

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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-476]

Chemical Names of Previously Controlled Fentanyl-Related Substances

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Notification of chemical names of previously controlled substances.

SUMMARY: The Drug Enforcement Administration (DEA) is providing additional descriptive information with respect to five specific substances already covered by a temporary scheduling order that appeared in the Federal Register on February 6, 2018. That order placed fentanyl-related substances temporarily in schedule I of the Controlled Substances Act. The order further stated that if and when DEA identifies a specific new substance that falls under the definition of a fentanyl-related substance, the agency will publish in the Federal Register, and on the agency website, the chemical name of such substance. Consistent therewith, this document provides the chemical names of five substances that fall within the definition of fentanyl-related substances that were temporarily controlled under the scheduling order issued February 6, 2018.

DATES: This notification has the same effective period as the temporary scheduling order published on February 6, 2018 (83 FR 5188): February 6, 2018 through February 6, 2020.

FOR FURTHER INFORMATION CONTACT: Lynnette M. Wingert, Diversion Control

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Division, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (202) 598-6812.

SUPPLEMENTARY INFORMATION: On February 6, 2018, DEA issued an order pursuant to **21 U.S.C. 811**(h), which temporarily placed fentanyl-related substances in schedule I of the Controlled Substances Act (CSA). 83 FR 5188. As defined in the order, fentanyl-related substances include any substance not otherwise controlled in any schedule (i.e., not included under any other Administration Controlled Substance Code Number) that is structurally related to fentanyl by one or more of the following modifications:

1. Replacement of the phenyl portion of the phenethyl group by any monocycle, whether or not further substituted in or on the monocycle;

2. substitution in or on the phenethyl group with alkyl, alkenyl, alkoxyl, hydroxyl, halo, haloalkyl, amino or nitro groups;

3. substitution in or on the piperidine ring with alkyl, alkenyl, alkoxyl, ester, ether, hydroxyl, halo, haloalkyl, amino or nitro groups;

4. replacement of the aniline ring with any aromatic monocycle whether or not further substituted in or on the aromatic monocycle; and/or

5. replacement of the *N*-propionyl group by another acyl group. The order further stated that if and when DEA identifies a specific new substance that falls under the definition of a fentanyl-related substance, the agency will publish in the Federal Register, and on the agency website, the chemical name of such substance. Consistent therewith, DEA is hereby providing the chemical names of five substances, which have been identified on the illicit market in the United States, that fall within the existing definition of a fentanyl-related substance:

N-(1-(2-fluorophenethyl)piperidin-4-yl)-*N*-(2-fluorophenyl)propionamide (2'-fluoro *ortho*-fluorofentanyl);

N-(2-methylphenyl)-*N*-(1-phenethylpiperidin-4-yl)acetamide (*ortho*-methyl acetylfentanyl);

N-(1-phenethylpiperidin-4-yl)-*N*,3-diphenylpropanamide (beta'-phenyl fentanyl; hydrocinnamoyl fentanyl);

N-(1-phenethylpiperidin-4-yl)-*N*-phenylthiophene-2-carboxamide (thiofuranyl fentanyl); and

(E)-*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylbut-2-enamide (crotonyl fentanyl).

The five foregoing substances fall within the definition of fentanyl-related substances as they are not otherwise listed under another Administration Controlled Substance Code Number and are structurally related to fentanyl by the following modifications:

2'-fluoro *ortho*-fluorofentanyl: Substitution on the phenethyl group with a halo group and substitution on the aniline ring (meets definition for modifications 2 and 4);

ortho-methyl acetylfentanyl: Substitution on the aniline ring and replacement of the *N*-propionyl group with another acyl group (meets definition for modifications 4 and 5);

beta'-phenyl fentanyl: Replacement of the *N*-propionyl group by another acyl group (meets definition for modification 5);

thiofuranyl fentanyl: Replacement of the *N*-propionyl group by another acyl group (meets definition for modification 5);

crotonyl fentanyl: Replacement of the *N*-propionyl group by another acyl group (meets definition for modification 5).

It bears emphasis that, as DEA stated in the temporary scheduling order for fentanyl-related substances, even in the absence of this publication providing the chemical names of the foregoing five substances that fall within the definition of a fentanyl-related substance, these five substances (along with any others that might be identified in the future) were controlled as of February 6, 2018 by virtue of the temporary scheduling order that DEA issued on that date. 83 FR 5188.

Dated: April 3, 2019.

Uttam Dhillon,
Acting Administrator.

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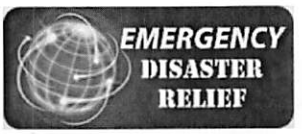

Rules - 2019

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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-491]

Schedules of Controlled Substances: Temporary Placement of 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA, and FUB-144 into Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Temporary amendment; temporary scheduling order.

SUMMARY: The Acting Administrator of the Drug Enforcement Administration is issuing this temporary scheduling order to schedule the synthetic cannabinoids (SC), ethyl 2-(1-(5-fluoropentyl)-1H-indazole-3-carboxamido)-3,3-dimethylbutanoate (trivial name: 5F-EDMB-PINACA); methyl 2-(1-(5-fluoropentyl)-1H-indole-3-carboxamido)-3,3-dimethylbutanoate (trivial name: 5F-MDMB-PICA); N-(adamantan-1-yl)-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide (trivial names: FUB-AKB48; FUB-APINACA; AKB48 N-(4-FLUOROBENZYL)); 1-(5-fluoropentyl)-N-(2-phenylpropan-2-yl)-1H-indazole-3-carboxamide (trivial names: 5F-CUMYL-PINACA; SGT-25); and (1-(4-fluorobenzyl)-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl) methanone (trivial name: FUB-144), and their optical, positional, and geometric isomers, salts, and salts of isomers in

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schedule I. This action is based on a finding by the Acting Administrator that the placement of these SCs in schedule I of the Controlled Substances Act is necessary to avoid an imminent hazard to the public safety. As a result of this order, the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances will be imposed on persons who handle (manufacture, distribute, reverse distribute, import, export, engage in research, conduct instructional activities or chemical analysis, or possess), or propose to handle, 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA or FUB-144.

DATES: This temporary scheduling order is effective April 16, 2019, until April 16, 2021. If this order is extended or made permanent, the DEA will publish a document in the Federal Register.

FOR FURTHER INFORMATION CONTACT: Lynnette M. Wingert, Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (202) 598-6812.

SUPPLEMENTARY INFORMATION:

Legal Authority

Section 201 of the Controlled Substances Act (CSA), **21 U.S.C. 811**, provides the Attorney General with the authority to temporarily place a substance in schedule I of the CSA for two years without regard to the requirements of 21 U.S.C. 811(b) if he finds that such action is necessary to avoid an imminent hazard to the public safety. 21 U.S.C. 811(h)(1). In addition, if proceedings to control a substance are initiated under 21 U.S.C. 811(a)(1), the Attorney General may extend the temporary scheduling \1\ for up to one year. 21 U.S.C. 811(h)(2).

\1\ Though DEA has used the term "final order" with respect to temporary scheduling orders in the past, this document adheres to the statutory language of **21 U.S.C. 811**(h), which refers to a "temporary scheduling order." No substantive change is intended.

Where the necessary findings are made, a substance may be temporarily scheduled if it is not listed in any other schedule under section 202 of the CSA, **21 U.S.C. 812**, or if there is no exemption or approval in effect for the substance under section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. 355. **21 U.S.C. 811**(h)(1). The Attorney General has delegated scheduling authority under 21 U.S.C. 811 to the Administrator of the DEA. 28 CFR 0.100.

Background

Section 201(h)(4) of the CSA, **21 U.S.C. 811**(h)(4), requires the Administrator to notify the Secretary of the Department of Health and Human Services (HHS) of his intention to temporarily place a substance in schedule I of the CSA.\2\ The Acting Administrator transmitted notice of his intent to place 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144 in schedule I on a temporary basis to the Assistant Secretary for Health of HHS by letter dated August 24, 2018. The Assistant Secretary responded to this notice by letter dated September 6, 2018, and advised that based on a review by the Food and Drug Administration (FDA), there are currently no active investigational new drug applications or approved new drug applications for 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA or FUB-144. The Assistant Secretary also stated that the HHS has no objection to the temporary placement of 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144 in schedule I of the CSA. The DEA has taken into consideration the Assistant Secretary's comments as required by 21 U.S.C. 811(h)(4). 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144 are not currently listed in any schedule under the CSA, and no exemptions or approvals are in effect for 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA or FUB-144 under section 505 of the FDCA, 21 U.S.C. 355. The DEA has found that the control of 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144 in schedule I on a temporary basis is necessary to avoid an imminent hazard to the public safety, and as required by 21 U.S.C. 811(h)(1)(A), a notice of intent to temporarily schedule 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144 was published in the Federal Register on December 28, 2018. 83 FR 67166.

\2\ As discussed in a memorandum of understanding entered into by the Food and Drug Administration (FDA) and the National Institute on Drug Abuse (NIDA), the FDA acts as the lead agency within the HHS in carrying out the Secretary's scheduling responsibilities under the CSA, with the concurrence of NIDA. 50 FR 9518, Mar. 8, 1985. The Secretary of the HHS has delegated to the Assistant Secretary for Health of the HHS the authority to make domestic drug scheduling recommendations. 58 FR 35460, July 1, 1993.

To find that placing a substance temporarily in schedule I of the CSA is necessary to avoid an imminent hazard to the public safety, the Administrator is required to consider three of the eight factors set forth in section 201(c) of the CSA, **21 U.S.C. 811**(c): The substance's history and current pattern of abuse; the scope, duration and significance of abuse; and what, if any, risk there is to the public health. 21 U.S.C. 811(h)(3). Consideration of these factors includes actual abuse, diversion from legitimate channels, and clandestine importation, manufacture, or distribution. 21 U.S.C. 811(h)(3).

A substance meeting the statutory requirements for temporary scheduling may only be placed in schedule I. **21 U.S.C. 811**(h)(1). 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).

Available data and information for 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144, summarized below, indicate that these synthetic cannabinoids (SCs) 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. The DEA's three-factor analysis and the Assistant Secretary's September 6, 2018 letter are available in their entirety under the tab "Supporting Documents" of the public docket of this action at www.regulations.gov.

Synthetic Cannabinoids

The illicit use of SCs continues to cause severe adverse effects, overdoses and deaths in the United States. SCs are substances synthesized in laboratories that mimic the biological effects of delta-9-tetrahydrocannabinol (THC), the main psychoactive ingredient in marijuana. SCs were introduced to the designer drug market in several European countries as "herbal incense" before the initial encounter in the United States by U.S. Customs and Border Protection (CBP) in November 2008. Since 2009, misuse of SCs has escalated in the United States as evidenced by large numbers of law enforcement encounters of SCs applied onto plant material and in other designer drug products intended for human consumption. Recent hospital reports, scientific publications, and/or law enforcement reports demonstrate that 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA, FUB-144 and their associated designer drug products are being abused for their psychoactive properties (see DEA 3-Factor Analysis). As with many generations of SCs encountered since 2009, the abuse of 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-

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CUMYL-PINACA and FUB-144 is negatively impacting communities in the United States.

As noted by the DEA and CBP, SCs originate from foreign sources, such as China. Bulk powder substances are smuggled via common carrier into the United States and find their way to clandestine designer drug product manufacturing operations located in residential neighborhoods, garages, warehouses, and other similar destinations throughout the country. According to online discussion boards and law enforcement encounters, spraying or mixing the SCs with plant material provides a vehicle for the most common route of administration--smoking (using a pipe, a water pipe, or rolling the drug-laced plant material in cigarette papers).

5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144 have no accepted medical use in the United States. Use of 5F-MDMB-PICA, 5F-EDMB-PINACA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144 has been reported to result in adverse effects in humans in the United States (see DEA 3-Factor Analysis). In addition, there have been multiple law enforcement seizures of 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144 in the United States. Use of other SCs has resulted in signs of addiction and withdrawal. Based on the pharmacological similarities between 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144 and other SCs, these five SCs are likely to produce signs of addiction and withdrawal similar to those produced by other SCs.

5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144 are SCs that have pharmacological effects similar to the schedule I hallucinogen THC, and other temporarily and permanently controlled schedule I SCs. In addition, the misuse of 5F-CUMYL-PINACA, 5F-EDMB-PINACA and FUB-144 has been associated with multiple overdoses requiring emergency medical intervention (see DEA 3-Factor Analysis) while deaths have been reported that involved FUB-AKB48. With no approved medical use and limited safety or toxicological information, 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144 have emerged in the designer drug market, and the abuse of these substances for their psychoactive properties is concerning.

Factor 4. History and Current Pattern of Abuse

SCs have been developed by researchers over the last 30 years as tools for investigating the endocannabinoid system (e.g., determining CB1 and CB2 receptor activity). The first encounter of SCs intended for illicit use within the United States occurred in November 2008 by CBP. Since then, the popularity of SCs as product adulterants and objects of abuse has increased as evidenced by law enforcement seizures, public health information, and media reports.

Numerous SCs have been identified as product adulterants, and law enforcement has seized bulk amounts of these substances. As successive generations of SCs have been identified and controlled as schedule I substances, illicit distributors have developed new SC substances that vary only by slight modifications to their chemical structure while retaining pharmacological effects related to their abuse potential. These substances, and products laced with these substances, are marketed under the guise of "herbal incense" and promoted as a "legal high" with a disclaimer that they are "not for human consumption." Thus, after section 1152 of the Food and Drug Administration Safety and Innovation Act (FDASIA), Public Law 112-144, placed cannabimimetic agents and 26 specific substances (15 of these are SCs) into schedule I, law enforcement documented the emergence of new SCs including UR-144, XLR11, AKB48, PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA. After these substances were temporarily scheduled (78 FR 28735, May 16, 2013; 79 FR 7577, February 10, 2014) other generations of SCs appeared and were temporarily controlled, including AB-CHMINACA, AB-PINACA, THJ-2201 (80 FR 5042, January 30, 2015), MAB-CHMINACA (81 FR 6171, February 5, 2016), 5F-ADB, 5F-AMB, 5F-ABK48, ADB-FUBINACA, MDMB-CHMICA, MDMB-FUBINACA (82 FR 17119, April 10, 2017), FUB-AMB (82 FR 51154, November 3, 2017) NM2201, 5F-AB-PINACA, 4-CN-CUMYL-BUTINACA, MMB-CHMICA and 5F-CUMYL-P7AICA (83 FR 31877, July 10, 2018).

FUB-AKB48 was first identified in seized drug evidence in October 2013, followed by FUB-144 (January 2014), 5F-MDMB-PICA (October 2016), 5F-EDMB-PINACA (October 2017) and 5F-CUMYL-PINACA (February 2018). Following their manufacture in China, SCs are often encountered in countries including New Zealand, Australia, and Russia before appearing throughout Europe, and eventually in the United States. 5F-CUMYL-PINACA was first reported in the German and Swiss illicit drug markets in 2015 but didn't show up in the United States until February 2018; 5F-EDMB-PINACA was reported in China in 2016 but didn't appear in the United States until October 2017; and 5F-MDMB-PICA was reported in Germany in August 2016 and November 2016 in Belgium, a few months before showing up in the United States. These data further support that based upon trends, SCs appear in the illicit drug markets of other countries including those in Europe, often before being trafficked in the United States. The misuse of 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144 has been associated with law enforcement seizures, overdoses requiring emergency medical intervention, or both (see DEA 3-Factor Analysis).

The powder form of SCs is typically dissolved in solvents (e.g., acetone) before being applied to plant material, or dissolved in a propellant intended for use in electronic cigarette devices. In addition, 5F-EDMB-PINACA was identified as an adulterant on pieces of paper that were smuggled into a detention facility and later found partially burned (see DEA 3--Factor Analysis). Law enforcement personnel have encountered various application methods including buckets or cement mixers in which plant material and one or more SCs are mixed together, or in large areas where the plant material is spread out so that a dissolved SC mixture can be applied directly. Once mixed, the SC plant material is then allowed to dry before manufacturers package the product for distribution, ignoring any control mechanisms to prevent contamination or to ensure a uniform concentration of the substance in each package. Adverse health consequences may also occur from directly ingesting the drug during the manufacturing process. The failure to adhere to any manufacturing standards with regard to amounts, the substance(s) included, purity, or contamination may increase the risk of adverse events. However, it is important to note that adherence to manufacturing standards would not eliminate their potential to produce adverse effects because the toxicity and safety profile of these SCs have not been studied.

5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144, similar to other SCs, have been found in powder form or mixed with dried leaves or herbal blends are marketed under the guise of "herbal

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incense" and promoted as "legal high" with disclaimer that they are "not for human consumption." Presentations at emergency departments directly linked to the abuse of 5F-EDMB-PINACA and FUB-144 have included seizures, agitation, vomiting, tachycardia and elevated blood pressure (see DEA 3-Factor Analysis).

Factor 5. Scope, Duration and Significance of Abuse

SCs continue to be encountered in the illicit market despite scheduling actions that attempt to safeguard the public from the adverse effects and safety issues associated with these substances (see DEA 3-Factor Analysis). Novel substances continue to be encountered, differing only by small chemical structural modifications intended to avoid prosecution while maintaining the pharmacological effects. Law enforcement and health care professionals continue to report the abuse of these substances and their associated products.

As described by NIDA, many substances being encountered in the illicit market, specifically SCs, have been available for years but have reentered the marketplace due to a renewed popularity. The threat of serious injury to the individual and the imminent threat to public safety following the ingestion of 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144 and other SCs persist.

Full reports of information obtained through STARLIMS,\3\ STRIDE,\4\ and NFLIS \5\ for the past five years may be found in the DEA 3-Factor Analysis. According to NFLIS, STARLIMS and STRIDE data, forensic laboratories have detected the following information about the SCs in question:

\3\ STARLIMS is a laboratory information management system that systematically collects results from drug chemistry analyses conducted by DEA laboratories. On October 1, 2014, STARLIMS replaced System to Retrieve Information from Drug Evidence (STRIDE) as the DEA laboratory drug evidence data system of record.

\4\ STRIDE is a database of drug exhibits sent to DEA laboratories for analysis. Exhibits from the database are from the DEA, other federal agencies, and some local law enforcement agencies.

\5\ The National Forensic Laboratory Information System (NFLIS) is a national forensic laboratory reporting system that systematically collects results from drug chemistry analyses conducted by State and local forensic laboratories in the United States.

- 5F-EDMB-PINACA was identified in 366 different NFLIS reports from eight states, since 2017 \6\ and 22 STRIDE/STARLIMS reports from two states, since 2017.

\6\ At the time of query, 2018 data were still reporting.

- 5F-MDMB-PICA was identified in 381 NFLIS reports from 22 states, since 2016 and 32 STRIDE/STARLIMS reports from seven states and the District of Columbia, since 2017.
- FUB-AKB48 was identified in 362 NFLIS reports from 21 states, since 2014 and 37 STRIDE/STARLIMS reports from eight states, since 2014.
- 5F-CUMYL-PINACA was identified in 54 NFLIS reports from three states, since 2018.
- FUB-144 was identified in 403 NFLIS reports from 27 states, since 2014 and 79 STARLIMS reports from 14 states plus Washington, DC, since 2014.

Factor 6. What, if Any, Risk There Is to the Public Health

Since first being identified in the United States in 2008, the ingestion of SCs continues to result in serious adverse effects. Details of these events involving 5F-CUMYL-PINACA, 5F-EDMB-PINACA, FUB-144, FUB-AKB48 and 5F-MDMB-PICA are summarized below.

1. In 2015, in London (United Kingdom), a 34-year-old male was hospitalized after ingesting a synthetic cannabinoid product. Toxicological analysis identified 5F-AKB48 and 5F-CUMYL-PINACA in biological samples.

2. In late November and early December 2015, in Jackson, Mississippi, five individuals presented at local emergency facilities following ingestion of a synthetic cannabinoid-containing product. Evidence collected from the individuals tested positive for THC, MAB-CHMINACA and FUB-144. Toxicological analysis of biological samples in all five patients identified THC, MAB-CHMINACA, and FUB-144.

3. In March 2017, in Chaves, New Mexico, a 14-year-old female was found in the bathroom of her home with seizure-like activity. Following transport to a local hospital by family members, she was pronounced dead approximately 20 minutes later. Toxicological analysis upon autopsy identified three SCs: FUB-AKB48, AB-CHMINACA, and ADB-CHMINACA (MAB-CHMINACA). The cause of death was determined to be toxic effects of synthetic cannabinoids (FUB-AKB48, AB-CHMINACA, and ADB-CHMINACA).

4. In January 2018, in Pittsburgh, Pennsylvania, 13 correctional facility workers were treated for overdose symptoms including diaphoresis, hypertension and tachycardia following ingestion of an airborne substance while conducting cell searches for contraband. In response to the overdose events, evidence retrieved from the searches tested positive for the synthetic cannabinoids 5F-ADB, 5F-EDMB-PINACA, and 4-CN-CUMYL-BUTINACA.

5. In March 2018, in Chicago, Illinois, a 22-year-old male expired at a local hospital. Toxicological analysis confirmed buprenorphine, brodifacoum, bromadiolone, FUB-AMB and FUB-AKB48 in biological samples of this decedent.

6. In April 2018, in Harrisburg, Pennsylvania, a 38-year-old male presented at a local hospital due to repeated nosebleeds, gastrointestinal bleeding with anemia and bruising on his arms. Toxicological analysis confirmed brodifacoum, FUB-AMB, and FUB-AKB48 in biological samples.

7. In April 2018, in Harrisburg, Pennsylvania, another patient presented at a local hospital due to significant bleeding and anemia requiring a transfusion. Toxicological analysis confirmed brodifacoum, FUB-AMB, and FUB-AKB48 in biological samples.

8. In June 2018, in Chicago, Illinois, a 25-year-old male expired at a local hospital. Toxicological analysis confirmed brodifacoum, bromadiolone, FUB-AMB and FUB-AKB48 in biological samples of this decedent.

9. In July 2018, in Washington, DC, in excess of 260 overdoses and four deaths were reported following use of a synthetic cannabinoid product. Analysis of drug evidence from the overdose event confirmed the presence of the synthetic cannabinoids FUB-AMB, EMB-FUBINACA and FUB-144.

10. In August 2018, in New Haven, Connecticut, in excess of 47 overdoses were reported following the use of a synthetic cannabinoid product. Analysis of drug evidence from the overdose event confirmed the presence of the synthetic cannabinoids 5F-ADB, FUB-AMB and 5F-MDMB-PICA.

11. In September 2018, law enforcement in Georgia seized multiple electronic cigarettes with various colored viscous liquids following the reports of overdoses. Laboratory analysis on the seized evidence determined the substance to be 5F-CUMYL-PINACA.

12. From September 10 to 16, 2018, in Washington, DC, at least 244 overdoses were reported following use of a synthetic cannabinoid product. Analysis of drug evidence from the overdose event confirmed the presence of the synthetic cannabinoids FUB-AMB and 5F-MDMB-PICA.

Because they share pharmacological similarities with schedule I substances ([Delta]\9\-THC, JWH-018 and other temporarily and permanently controlled schedule I SCs), 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-

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PINACA, and FUB-144 pose serious risks to an abuser. Tolerance to SCs may develop fairly rapidly with larger doses being required to achieve the desired effect. Acute and chronic abuse of SCs in general have been linked to adverse health effects including signs of addiction and withdrawal, numerous reports of emergency department admissions, and overall toxicity and deaths. Psychiatric case reports have been reported in the scientific literature detailing the SC abuse and associated psychoses. As abusers obtain these drugs through unknown sources, the identity and purity of these substances is uncertain and inconsistent, thus posing significant adverse health risks to users.

5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144 are being encountered on the illicit drug market and have no accepted medical use in the United States. Regardless, these products continue to be easily available and abused by diverse populations.

Finding of Necessity of Schedule I Placement To Avoid Imminent Hazard to Public Safety

In accordance with **21 U.S.C. 811(h)(3)**, based on the available data and information summarized above, the continued uncontrolled manufacture, distribution, reverse distribution, importation, exportation, conduct of research and chemical analysis, possession, and abuse of 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144 pose an imminent hazard to the public safety. The DEA is not aware of any currently accepted medical uses for 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA or FUB-144 in the United States. A substance meeting the statutory requirements for temporary scheduling, 21 U.S.C. 811(h)(1), may only be placed in schedule I. 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. Available data and information for 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144 indicate that these SCs 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. As required by section 201(h)(4) of the CSA, 21 U.S.C. 811(h)(4), the Acting Administrator, through a letter dated August 24, 2018, notified the Assistant Secretary of the DEA's intention to temporarily place 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144 in schedule I. A notice of intent was subsequently published in the Federal Register on December 28, 2018. 83 FR 67166.

Conclusion

In accordance with the provisions of section 201(h) of the CSA, **21 U.S.C. 811(h)**, the Acting Administrator considered available data and information, and herein sets forth the grounds for his determination that it is necessary to temporarily schedule ethyl 2-(1-(5-fluoropentyl)-1H-indazole-3-carboxamido)-3,3-dimethylbutanoate (trivial name: 5F-EDMB-PINACA); methyl 2-(1-(5-fluoropentyl)-1H-indole-3-carboxamido)-3,3-dimethylbutanoate (trivial name: 5F-MDMB-PICA); N-(adamantan-1-yl)-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide (trivial names: FUB-AKB48; FUB-APINACA; AKB48 N-(4-FLUOROBENZYL)); 1-(5-fluoropentyl)-N-(2-phenylpropan-2-yl)-1H-indazole-3-carboxamide (trivial names: 5F-CUMYL-PINACA; SGT-25); and (1-(4-fluorobenzyl)-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (trivial name: FUB-144) in schedule I of the CSA to avoid an imminent hazard to the public safety.

Because the Acting Administrator hereby finds it necessary to temporarily place 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144 in schedule I to avoid an imminent hazard to the public safety, this temporary order scheduling these substances is effective on the date of publication in the Federal Register, and is in effect for a period of two years, with a possible extension of one additional year, pending completion of the regular (permanent) scheduling process. **21 U.S.C. 811(h)(1) and (2).**

The CSA sets forth specific criteria for scheduling a drug or other substance. Permanent scheduling actions in accordance with **21 U.S.C. 811(a)** are subject to formal rulemaking procedures done "on the record after opportunity for a hearing" conducted pursuant to the provisions of 5 U.S.C. 556 and 557. 21 U.S.C. 811. The permanent scheduling process of formal rulemaking affords interested parties with appropriate process and the government with any additional relevant information needed to make a determination. Final decisions that conclude the permanent scheduling process of formal rulemaking are subject to judicial review. **21 U.S.C. 877.** Temporary scheduling orders are not subject to judicial review. 21 U.S.C. 811(h)(6).

Requirements for Handling

Upon the effective date of this temporary order, 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144 will be subject to the regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, reverse distribution, importation, exportation, engagement in research, and conduct of instructional activities or chemical analysis with, and possession of schedule I controlled substances including the following:

1. *Registration.* Any person who handles (manufactures, distributes, reverse distributes, imports, exports, engages in research, or conducts instructional activities or chemical analysis with, or possesses), or who desires to handle, 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA or FUB-144 must be registered with the DEA to conduct such activities pursuant to **21 U.S.C. 822, 823, 957,** and **958,** and in accordance with **21 CFR parts 1301** and **1312,** as of April 16, 2019. Any person who currently handles 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA or FUB-144, and is not registered with the DEA, must submit an application for registration and may not continue to handle 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA or FUB-144 as of April 16, 2019, unless the DEA has approved that application for registration pursuant to 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312. Retail sales of schedule I controlled substances to the general public are not allowed under the CSA. Possession of any quantity of these substances in a manner not authorized by the CSA on or after April 16, 2019 is unlawful and those in possession of any quantity of these substances may be subject to prosecution pursuant to the CSA.

2. *Disposal of stocks.* Any person who does not desire or is not able to obtain a schedule I registration to handle 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA or FUB-144 must surrender all currently held quantities of 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA or FUB-144.

3. *Security.* 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144 are subject to schedule I security requirements and must be handled and stored pursuant to **21 U.S.C. 821, 823, 871(b),** and in

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accordance with **21 CFR 1301.71-1301.93,** as of April 16, 2019.

4. *Labeling and Packaging.* All labels, labeling, and packaging for commercial containers of 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA or FUB-144 must be in compliance with **21 U.S.C. 825, 958(e),** and be in accordance with **21 CFR part 1302.** Current DEA registrants shall have 30 calendar days from April 16, 2019, to comply with all labeling and packaging requirements.

5. *Inventory.* Every DEA registrant who possesses any quantity of 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA or FUB-144 on the effective date of this order must take an inventory of all stocks of these substances on hand, pursuant to **21 U.S.C. 827** and **958,** and in accordance with **21 CFR 1304.03, 1304.04,** and **1304.11.** Current DEA registrants shall have 30 calendar days from the effective date of this order to be in compliance with all inventory requirements. After the initial inventory, every DEA registrant must take an inventory of all controlled substances (including 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144) on hand on a biennial basis, pursuant to 21 U.S.C. 827 and 958, and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11.

6. *Records.* All DEA registrants must maintain records with respect to 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB-144 pursuant to **21 U.S.C. 827** and **958(e),** and in accordance with **21 CFR parts 1304, 1312, 1317** and **Sec. 1307.11.** Current DEA registrants authorized to handle 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA or FUB-144 shall have 30 calendar days from the effective date of this order to be in compliance with all recordkeeping requirements.

7. *Reports.* All DEA registrants who manufacture or distribute 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA or FUB-144 must submit reports pursuant to **21 U.S.C. 827** and in accordance with **21 CFR 1304** and **1312** as of April 16, 2019.

8. *Order Forms.* All DEA registrants who distribute 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA or FUB-144 must comply with order form requirements pursuant to **21 U.S.C. 828** and in accordance with **21 CFR part 1305** as of April 16, 2019.

9. *Importation and Exportation.* All importation and exportation of 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA or FUB-144 must be in compliance with **21 U.S.C. 952, 953, 957, 958,** and in accordance with **21 CFR part 1312** as of April 16, 2019.

10. *Quota.* Only DEA registered manufacturers may manufacture 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA or FUB-144 in accordance with a quota assigned pursuant to **21 U.S.C. 826** and in accordance with **21 CFR part 1303** as of April 16, 2019.

11. *Liability.* Any activity involving 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA or FUB-144 not authorized by, or in violation of the CSA, occurring as of April 16, 2019, is unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

Regulatory Matters

Section 201(h) of the CSA, **21 U.S.C. 811(h),** provides for a temporary scheduling action where such action is necessary to avoid an imminent hazard to the public safety. As provided in this subsection, the Attorney General may, by order, schedule a substance in schedule I on a temporary basis. Such an order may not be issued before the expiration of 30 days from (1) the publication of a notice in the Federal Register of the intention to issue such order and the grounds upon which such order is to be issued, and (2) the date that notice of the proposed temporary scheduling order is transmitted to the Assistant Secretary. 21 U.S.C. 811(h)(1).

Inasmuch as section 201(h) of the CSA directs that temporary scheduling actions be issued by order (as distinct from a rule) and sets forth the procedures by which such orders are to be issued, the DEA believes that the notice and comment requirements of section 553 of the Administrative Procedure Act (APA), 5 U.S.C. 553, which are applicable to rulemaking, do not apply to this temporary scheduling order. The specific language chosen by Congress indicates an intention for the DEA to proceed through the issuance of an order instead of proceeding by rulemaking. Given that Congress specifically requires the Attorney General to follow rulemaking procedures for other kinds of scheduling actions, see section 201(a) of the CSA, **21 U.S.C. 811(a),** it is noteworthy that, in section 201(h), Congress authorized the issuance of temporary scheduling actions by order rather than by rule.

In the alternative, even assuming that this action might be subject to 5 U.S.C. 553, the Administrator finds that there is good cause to forgo the notice and comment requirements of section 553, as any further delays in the process for issuance of temporary scheduling orders would be impracticable and contrary to the public interest in view of the manifest urgency to avoid an imminent hazard to the public safety.

Further, the DEA believes that this temporary scheduling action is not a "rule" as defined by 5 U.S.C. 601(2), and, accordingly, is not subject to the requirements of the Regulatory Flexibility Act. The requirements for the preparation of an initial regulatory flexibility analysis in 5 U.S.C. 603(a) are not applicable where, as here, the DEA is not required by the APA or any other law to publish a general notice of proposed rulemaking.

Additionally, this action is not a significant regulatory action as defined by Executive Order 12866 (Regulatory Planning and Review), section 3(f), and, accordingly, this action has not been reviewed by the Office of Management and Budget.

This action will not have substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government. Therefore, in accordance with Executive Order 13132 (Federalism) it is determined that this action does not have sufficient federalism implications to warrant the preparation of a Federalism Assessment.

As noted above, this action is an order, not a rule. Accordingly, the Congressional Review Act (CRA) is inapplicable, as it applies only to rules. However, if this were a rule, pursuant to the CRA, "any rule for which an agency for good cause finds that notice and public procedure thereon are impracticable, unnecessary, or contrary to the public interest, shall take effect at such time as the federal agency promulgating the rule determines." 5 U.S.C. 808(2). It is in the public interest to schedule these substances immediately to avoid an imminent hazard to the public safety. This temporary scheduling action is taken pursuant to **21 U.S.C. 811(h),** which is specifically designed to enable the DEA to act in an expeditious manner to avoid an imminent hazard to the public safety. 21 U.S.C. 811(h) exempts the temporary scheduling order from standard notice and comment rulemaking procedures to ensure that the process moves swiftly. For the same reasons that underlie 21 U.S.C. 811(h), that is, the DEA's need to move quickly to place these substances in schedule I because they pose an imminent hazard to the public safety, it would be contrary to the public interest to delay implementation of the temporary scheduling order. Therefore, this order shall take effect immediately

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upon its publication. The DEA has submitted a copy of this temporary order to both Houses of Congress and to the Comptroller General, although such filing is not required under the Small Business Regulatory Enforcement Fairness Act of 1996 (Congressional Review Act), 5 U.S.C. 801-808 because, as noted above, this action is an order, not a rule.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, the DEA amends 21 CFR part 1308 as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

- 1. The authority citation for part 1308 continues to read as follows:

  Authority: 21 U.S.C. 811, 812, 871(b), 956(b), unless otherwise noted.

- 2. In **Sec. 1308.11,** add paragraphs (h)(37) through (41) to read as follows:

Sec. 1308.11 Schedule I.

* * * * *

(h) * * *

(37) ethyl 2-(1-(5-fluoropentyl)-1*H*-indazole-3-carboxamido)-3,3-dimethylbutanoate, its optical, positional, and geometric isomers, salts and salts of isomers (trivial name: 5F-EDMB-PINACA)	7036
(38) methyl 2-(1-(5-fluoropentyl)-1*H*-indole-3-carboxamido)-3,3-dimethylbutanoate, its optical, positional, and geometric isomers, salts and salts of isomers (trivial name: 5F-MDMB-PICA)	7041
(39) *N*-(adamantan-1-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide, its optical, positional, and geometric isomers, salts and salts of isomers (trivial names: FUB-AKB48; FUB-APINACA; AKB48 N-(4-FLUOROBENZYL))	7047
(40) 1-(5-fluoropentyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide, its optical, positional, and geometric isomers, salts and salts of isomers (trivial names: 5F-CUMYL-PINACA; SGT-25)	7083
(41) (1-(4-fluorobenzyl)-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl) methanone, its optical, positional, and geometric isomers, salts and salts of isomers (trivial name: FUB-144)	7014

Dated: April 5, 2019.

Uttam Dhillon,
Acting Administrator.

[FR Doc. 2019-07460 Filed 4-15-19; 8:45 am]

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DIVERSION CONTROL DIVISION

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Drug Enforcement Administration
Diversion Control Division
Drug & Chemical Evaluation Section

Etizolam

(Trade Names: Etilaam, Etizest, Depas, Etizola, Sedekopan, Pasaden)

March 2020

Introduction:

Etizolam is a thienodiazepine which is chemically related to a class of substances known as benzodiazepines. Benzodiazepines produce central nervous system (CNS) depression and are commonly used to treat insomnia and anxiety. Etizolam is currently a prescription medication in Japan, India and Italy but has recently emerged on the illicit drug market in Europe and the United States.

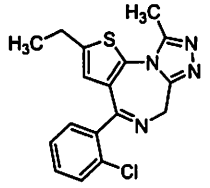
Etizolam is usually encountered in powder form or in tablet form. Etizolam has also been encountered spiked onto blotter paper.

Licit Uses:

Benzodiazepines are widely prescribed drugs; however, etizolam is not approved for medical use in the United States. Additionally, etizolam is used as a prescription medication in some countries. Etizolam was introduced in 1983 in Japan as a treatment for neurological conditions such as anxiety and sleep disorders. It is currently available as 0.25 mg, 0.5 mg and 1.0 mg tablets in countries where it is marketed for clinical use.

Chemistry:

Etizolam (4-(2-chlorophenyl)-2-ethyl-9-methyl-6*H*thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine) has a similar structure to the benzodiazepine class of compounds. Etizolam has a thiophene ring, in place of a benzene ring found in the benzodiazepine class, fused to a seven-membered 1,4diazepine ring. Etizolam also contains a fused triazolo ring. A 2-chlorophenyl ring is attached at the 4-position and an ethyl group is attached at the 2-position of the thienodiazepine ring structure. Etizolam has a molecular formula of $C_{17}H_{15}ClN_4S$ and a molecular weight of 342.8 g/mol. The structure of etizolam is shown below:



Pharmacology:

Etizolam, a thienodiazepine derivative, was approved for the management of anxiety disorders associated with depression, panic disorder and insomnia in some countries. Pharmacologically, etizolam is a benzodiazepine and possesses CNS depressant effects, such as anxiolytic, anticonvulsant, sedative-hypnotic and muscle relaxant effects. Unlike diazepam (Valium®), it has some imipramine-like neuropharmacological and behavioral effects in preclinical studies. In animal experiments, etizolam is 6-10 times more potent than diazepam in most of its pharmacological effects. Etizolam has been demonstrated to have some reinforcing effects in monkeys. In physical-dependence studies in animals, it substituted for barbital and produced withdrawal signs typical of the sedative-hypnotic class. Drug discrimination studies in monkeys indicated that it had pentobarbital-like effects. Clinical studies suggest that etizolam is approximately 10 times as potent as diazepam in producing hypnotic effects. In a single-dose pharmacokinetic study in humans, etizolam was rapidly absorbed with the maximum plasma concentration occurring within 0.5-2 hours and the mean elimination half-life averaged 3.4 hours. Clinical observations of physical dependence on etizolam were also reported. Major adverse effects include drowsiness, sedation, muscle weakness and incoordination, fainting, headache, confusion, depression, slurred speech, visual disturbances and changes in libido and tremor.

Illicit Uses:

In recent years there has been a rise in the abuse of etizolam. In September 2014, the Blue Ridge Poison Center called etizolam an emerging drug of concern. Additionally they stated there has been an upward trend in Poison Control Center calls.

User Population:

Although it is a legitimate pharmaceutical product in Japan, Italy and India, etizolam is used as a recreational substance in the United States. Information suggests that a broad range of populations including youths, young adults and older adults, use etizolam.

Illicit Distribution:

Etizolam is purchased via the internet and at local retail shops where it is promoted as a "research chemical." It has been sold as a powder, in tablet form and spiked onto blotter paper. The National Forensic Laboratory Information System (NFLIS) is a DEA database that collects scientifically verified data on drug items and cases submitted to and analyzed by state, local, and federal forensic laboratories. The System to Retrieve Information from Drug Evidence (STRIDE)/STARLiMS provides information on drug seizures reported to and analyzed by DEA laboratories. According to NFLIS, the number of etizolam drug reports have steadily increased from 3 in 2012, to 600 reports in 2016, 950, in 2017, and 1,570 in 2018. In the first nine months of 2019, there were 953 drug reports of etizolam submitted within the NFLIS database, in which roughly 4,870 reports were from 46 states from 2012 through September of 2019. There were no reports of etizolam in NFLIS and/or STRIDE/STARLiMS prior to 2012.

Control Status:

Etizolam is not currently controlled under the Controlled Substances Act.

Comments and additional information are welcomed by the Drug and Chemical Evaluation Section; Fax 571-362-4250, Telephone 571-362-3249, or Email DPE@usdoj.gov.

DEA PRB 03-24-20-11

Drug Enforcement Administration
Diversion Control Division
Drug & Chemical Evaluation Section

June 2020

FLUALPRAZOLAM
(Street Name: Flualp)

Introduction:

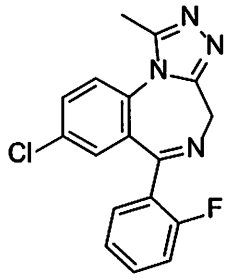
Flualprazolam is structurally related to the triazolo-benzodiazepine, alprazolam. As a class of drugs, benzodiazepines produce central nervous system (CNS) depression and are commonly used to treat, panic disorders, anxiety, and insomnia. The United States Food and Drug Administration has not approved flualprazolam for therapeutic use.

Licit Uses:

Flualprazolam does not currently have an accepted medical use in the United States.

Chemistry:

Flualprazolam (8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine) is a triazolobenzo-diazepine and is structurally similar to alprazolam. Flualprazolam is composed of a benzene ring fused to a seven-membered 1,4-diazepine ring. Flualprazolam also contains a fused triazolo ring. A methyl (-CH_3) group is attached at the 1-position, a 2-fluorophenyl ring is attached at the 6-position, and a chlorine is attached at the 8-position of the triazolobenzodiazepine structure. Flualprazolam has a molecular formula of $C_{17}H_{12}ClFN_4$ and a molecular weight of 326.76 g/mol. The structure of flualprazolam is shown below:



Pharmacology:

There is limited information regarding the pharmacology of flualprazolam in published literatures. Flualprazolam shares structural similarities with alprazolam and other Schedule IV benzodiazepines. Thus, it is likely to bind to benzodiazepine receptor sites and produce central nervous system depressant effects similar to that of alprazolam and other Schedule IV benzodiazepines. Although there are no studies regarding the effects of flualprazolam in humans, anecdotal online reports describe sedation and physical impairment following oral ingestion, which suggests, flualprazolam possesses central nervous system depressant effects similar to other known Schedule IV benzodiazepines. Recreational use of flualprazolam may result in prolonged, severe sedation associated with coma. The onset of action of flualprazolam following oral administration is reported to be 10-30 minutes. Flualprazolam has a long duration of action (6-14 hour) compared to the relatively short acting alprazolam.

According to the United Nations Office on Drugs and Crime (UNODC) Early Warning Advisory on NPS Toxicology Portal (Tox-Portal), an online tool utilized to collect toxicological data and harm associated with the use of novel psychoactive substances, 42 cases involving flualprazolam were reported in 2019. Of the 42 cases reported to UNODC, 40 cases originated from the United States. In five of these U.S. cases, flualprazolam was determined to be causal to the event that precipitated reporting.

Illicit Uses:

Flualprazolam is generally abused for its sedative/hypnotic effects. Reports from online drug user forums describe it to be similar to clonazepam and alprazolam.

User Population:

Flualprazolam is used as a recreational substance in the United States. It is generally abused by young adults, especially males.

Illicit Distribution:

Flualprazolam can be purchased via the internet as a research chemical. It is generally encountered in pill form and the external markings have been found to mimic that of Zanax and Klonopin. The National Forensic Laboratory Information System (NFLIS) is a DEA database that collects scientifically verified data on drug items and cases submitted to and analyzed by state, local, and federal forensic laboratories. According to NFLIS, the number of flualprazolam drug reports increased from one in 2017 to 112 in 2018 and, has continued to increase preliminarily to 1,624 in 2019.

The National Poison Data System (NPDS) of the American Association of Poison Control Centers (AAPCC) utilized by members of the public and health care providers reported no flualprazolam single substance exposures in 2014 and 2015, 2 exposures in 2018 and 11 in 2019. DEA would be appreciative of any toxicology or adverse event reporting connected to flualprazolam.

Control Status:

Flualprazolam is not currently controlled under the Controlled Substances Act. At the 2020 Commission on Narcotic Drugs Sixty-third session, the Commission decided to include flualprazolam in Schedule IV of the 1971 Convention on Psychotropic Substance.

Comments and additional information are welcomed by the Drug and Chemical Evaluation Section; Fax 571-362-4250, Telephone 571-362-3249, or email: DPE@usdoj.gov.

Drug Enforcement Administration
Diversion Control Division
Drug & Chemical Evaluation Section

FLUBROMAZOLAM
(Street Name: Liquid Xanax)

August 2019
DEA/DC/DO/DOE

Introduction

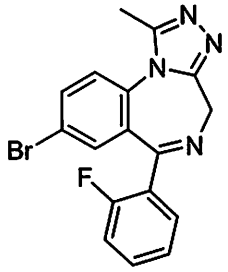
Flubromazolam is a triazole analogue of the designer benzodiazepine, flubromazepam. As a class of drugs, benzodiazepines produce central nervous system (CNS) depression and are commonly used to treat, panic disorders, anxiety and insomnia. The United States Food and Drug Administration has not approved Flubromazolam for therapeutic use.

Licit Uses

Flubromazolam does not currently have an accepted medical use in the United States.

Chemistry

Flubromazolam (8-bromo-6-(2-fluorophenyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine) is a triazole analogue of the benzodiazepine flubromazepam. Flubromazolam is composed of a benzene ring fused to a seven-membered 1,4-diazepine ring that is also fused to a 1,2,4 triazole ring. An alkyl methyl (-CH_3) is attached at the 1-position of the triazole ring, a 2-fluorophenyl ring is attached at the 6-position of the diazapine ring, and a bromine is attached at the 8-position of the benzene ring. Flubromazolam has a molecular formula of $C_{17}H_{12}BrFN_4$ and a molecular weight of 371.21 g/mol. The structure of flubromazolam is shown below:



Pharmacology

Flubromazolam, similar to schedule IV benzodiazepines (such as alprazolam, clonazepam, diazepam), binds to the benzodiazepine receptors with high affinity and efficacy. Flubromazolam possesses central nervous system depressant effects, such as anxiolytic, anticonvulsant, sedative-hypnotic and muscle relaxant effects. The recreational use of flubromazolam may result in prolonged, severe intoxication associated with coma, hypotension, and rhabdomyolysis (a breakdown of muscle tissue leading to release of dangerous protein into the bloodstream).

According to a published case report in which a 44 year-old investigator (weighing 75 kg) orally ingested a low dose (0.5 mg/day) of flubromazolam, sedative-hypnotic effects as well as muscle relaxant effects occurred 90 minutes following drug intake. Drowsiness occurred approximately three hours post-drug ingestion, and lasted for five hours. Intoxication due to flubromazolam is characterized by excessive drowsiness, partial amnesia and inability to follow or participate in conversation. Peak serum concentration of flubromazolam is reached approximately 5 hours (7.4 ng/mL) after administration with a second peak occurring after 8 hours (8.6 ng/mL), making it a long-acting benzodiazepine. In a single-dose pharmacokinetic study in humans, 30 hours following flubromazolam ingestion, a re-emergence of sedative effects was observed.

User Population

Flubromazolam is used as a recreational substance in the United States. It is abused by a broad range of groups including youths, young adults, and older adults.

Illicit Distribution

Flubromazolam can be purchased via the internet and at local retail shops. It has been identified in PEZ-like pills or tablets. The National Forensic Laboratory Information System (NFLIS) is a DEA database that collects scientifically verified data on drug items and cases submitted to and analyzed by state, local, and federal forensic laboratories. According to NFLIS, the number of flubromazolam drug reports increased from 14 in 2015 to 27 in 2016 and, has continued to increase to 261 in 2017. In 2018, there were 398 reports of flubromazolam in the NFLIS database.

The National Poison Data System (NPDS) of the American Association of Poison Control Centers (AAPCC) by members of the public and health care providers reported no flubromazolam single substance exposures in 2014 and 2015, 2 exposures in 2016 and 11 in 2017. In 2017, the UNODC Early Warning Advisory on Novel Psychoactive Substances mentioned flubromazolam in its report.

Control Status

Flubromazolam is not currently controlled under the Controlled Substances Act.

Comments and additional information are welcomed by the Drug and Chemical Evaluation Section; Fax 202-353-1263, telephone 202-307-7183, and Email DPE@usdoj.gov.

Rules - 2019

[Federal Register Volume 84, Number 138 (Thursday, July 18, 2019)]
[Rules and Regulations]
[Pages 34291-34297]
From the Federal Register Online via the Government Publishing Office [www.gpo.gov]
[FR Doc No: 2019-15184]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-495]

Schedules of Controlled Substances: Temporary Placement of *N*-Ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, and 4-Chloro-α-PVP in Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Temporary amendment; temporary scheduling order.

SUMMARY: The Acting Administrator of the Drug Enforcement Administration (DEA) is issuing this temporary scheduling order to schedule the synthetic cathinones, *N*-ethylhexedrone (2-(ethylamino)-1-phenylhexan-1-one); *alpha*-pyrrolidinohexanophenone (1-phenyl-2-(pyrrolidin-1-yl)hexan-1-one; *alpha*-pyrrolidinohexiophenone; trivial name: α-PHP); 4-methyl-*alpha*-ethylaminopentiophenone (2-(ethylamino)-1-(4-methylphenyl)pentan-1-one; trivial name: 4–MEAP); 4'-methyl-*alpha*-pyrrolidinohexiophenone (1-(4-methylphenyl)-2-(pyrrolidin-1-yl)hexan-1-one; 4'-methyl-*alpha*-pyrrolidinohexanophenone; trivial name: MPHP); *alpha*-pyrrolidinoheptaphenone (1-phenyl-2-(pyrrolidin-1-yl)heptan-1-one; trivial name: PV8); and 4'-chloro-*alpha*-pyrrolidinovalerophenone (1-(4-chlorophenyl)-2-(pyrrolidin-1-yl)pentan-1-one; 4'-chloro-*alpha*-pyrrolidinopentiophenone; trivial name: 4-chloro-α-PVP), and their optical, positional, and geometric isomers, salts, and salts of isomers in schedule I. This action is based on a finding by the Acting Administrator that the placement of these synthetic cathinones in schedule I of the Controlled Substances Act is necessary to avoid an imminent hazard to the public safety. As a result of this order, the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances will be imposed on persons who handle (manufacture, distribute, reverse distribute, possess, import, export, research, or conduct instructional activities or chemical analysis), or propose to handle, *N*-ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, and 4-chloro-α-PVP.

DATES: This temporary scheduling order is effective July 18, 2019, until July 18, 2021. If this order is extended or made permanent, the DEA will publish a document in the Federal Register.

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FOR FURTHER INFORMATION CONTACT: Scott A. Brinks, Regulatory Drafting and Policy Support Section (DPW), Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (202) 598-6812.

SUPPLEMENTARY INFORMATION:

Legal Authority

Section 201 of the Controlled Substances Act (CSA), **21 U.S.C. 811**, provides the Attorney General with the authority to temporarily place a substance in schedule I of the CSA for two years without regard to the requirements of 21 U.S.C. 811(b), if he finds that such action is necessary to avoid an imminent hazard to the public safety. 21 U.S.C. 811(h)(1). In addition, if proceedings to control a substance permanently are initiated under 21 U.S.C. 811(a)(1) while the substance is temporarily controlled under section 811(h), the Attorney General may extend the temporary scheduling \1\ for up to one year. 21 U.S.C. 811(h)(2).

\1\ Though DEA has used the term "final order" with respect to temporary scheduling orders in the past, this document adheres to the statutory language of **21 U.S.C. 811**(h), which refers to a "temporary scheduling order." No substantive change is intended.

Where the necessary findings are made, a substance may be temporarily scheduled if it is not listed in any other schedule under section 202 of the CSA, **21 U.S.C. 812**, or if there is no exemption or approval in effect for the substance under section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. 355. **21 U.S.C. 811**(h)(1); 21 CFR part 1308. The Attorney General has delegated scheduling authority under 21 U.S.C. 811 to the Administrator of the DEA. 28 CFR 0.100.

Background

Section 201(h)(4) of the CSA, **21 U.S.C. 811**(h)(4), requires the Administrator to notify the Secretary of the Department of Health and Human Services (HHS) of his intention to temporarily place a substance in schedule I of the CSA.\2\ The Acting Administrator transmitted notice of his intent to place *N*-ethylhexedrone; *alpha*-pyrrolidinohexanophenone (α-PHP); 4-methyl-*alpha*-ethylaminopentiophenone (4–MEAP); 4'-methyl-*alpha*-pyrrolidinohexiophenone (MPHP); *alpha*-pyrrolidinoheptaphenone (PV8); and 4-chloro-*alpha*-pyrrolidinovalerophenone (4-chloro-α-PVP) in schedule I on a temporary basis to the Assistant Secretary for Health of HHS by letter dated March 9, 2018. The Assistant Secretary responded to this notice of intent by letter dated March 27, 2018, and advised that based on a review by the Food and Drug Administration (FDA), there were currently no approved new drug applications or active investigational new drug applications for *N*-ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, and 4-chloro-α-PVP. The Assistant Secretary also stated that the HHS had no objection to the temporary placement of *N*-ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, and 4-chloro-α-PVP in schedule I of the CSA.

\2\ As discussed in a memorandum of understanding entered into by the Food and Drug Administration (FDA) and the National Institute on Drug Abuse (NIDA), the FDA acts as the lead agency within the HHS in carrying out the Secretary's scheduling responsibilities under the CSA, with the concurrence of NIDA. 50 FR 9518, Mar. 8, 1985. The Secretary of the HHS has delegated to the Assistant Secretary for Health of the HHS the authority to make domestic drug scheduling recommendations. 58 FR 35460, July 1, 1993.

The DEA has taken into consideration the Assistant Secretary's comments as required by **21 U.S.C. 811**(h)(4). *N*-Ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, and 4-chloro-α-PVP are not currently listed in any schedule under the CSA, and no exemptions or approvals are in effect for *N*-ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, and 4-chloro-α-PVP under section 505 of the FDCA, 21 U.S.C. 355. The DEA has found that the control of *N*-ethylhexedrone (2-(ethylamino)-1-phenylhexan-1-one); *alpha*-pyrrolidinohexanophenone (1-phenyl-2-(pyrrolidin-1-yl)hexan-1-one; *alpha*-pyrrolidinohexiophenone; trivial name: α-PHP); 4-methyl-*alpha*-ethylaminopentiophenone (2-(ethylamino)-1-(4-methylphenyl)pentan-1-one; trivial name: 4–MEAP); 4'-methyl-*alpha*-pyrrolidinohexiophenone (1-(4-methylphenyl)-2-(pyrrolidin-1-yl)hexan-1-one; 4'-methyl-*alpha*-pyrrolidinohexanophenone; trivial name: MPHP); *alpha*-pyrrolidinoheptaphenone (1-phenyl-2-(pyrrolidin-1-yl)heptan-1-

one; trivial name: PV8); and 4'-chloro-*alpha*-pyrrolidinovalerophenone (1-(4-chlorophenyl)-2-(pyrrolidin-1-yl)pentan-1-one; 4'-chloro-*alpha*-pyrrolidinopentiophenone; trivial name: 4-chloro-α-PVP) in schedule I on a temporary basis is necessary to avoid an imminent hazard to the public safety.

As required by **21 U.S.C. 811**(h)(1)(A), DEA published a notice of intent to temporarily schedule *N*-ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, and 4-chloro-α-PVP in the Federal Register on May 1, 2019 (84 FR 18423). That notice of intent identified the six substances using the common names; however, in the three-factor analysis, which DEA made available on www.regulations.gov contemporaneously with the publication of the notice of intent, these same substances were identified using the International Union of Pure and Applied Chemistry (IUPAC) nomenclature. This temporary scheduling order provides the common names, as well as the IUPAC names, for all six substances.

To find that placing a substance temporarily in schedule I of the CSA is necessary to avoid an imminent hazard to the public safety, the Administrator is required to consider three of the eight factors set forth in **21 U.S.C. 811**(c): The substance's history and current pattern of abuse; the scope, duration and significance of abuse; and what, if any, risk there is to the public health. 21 U.S.C. 811(h)(3). Consideration of these factors includes actual abuse, diversion from legitimate channels, and clandestine importation, manufacture, or distribution. 21 U.S.C. 811(h)(3).

A substance meeting the statutory requirements for temporary scheduling may only be placed in schedule I. **21 U.S.C. 811**(h)(1). 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).

Available data and information for *N*-ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, and 4-chloro-α-PVP, summarized below, indicate that these synthetic cathinones 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. The DEA's three-factor analysis and the Assistant Secretary's March 27, 2018 letter are available in their entirety under the tab "Supporting Documents" of the public docket of this action at www.regulations.gov.

Synthetic Cathinones

Novel synthetic cathinones that mimic the biological effects of substances with stimulant-like effects continue to emerge in the illicit drug market. These novel cathinones, also known as designer drugs, are structurally similar to several drugs of abuse such as schedule I synthetic cathinones (e.g., methcathinone, mephedrone, methylone, pentylone, and 3,4-methylenedioxypyrovalerone (MDPV)). The illicit use of synthetic cathinones has continued throughout the United States, resulting in severe adverse effects, overdoses, and deaths. Indeed, hospital reports, scientific

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publications, and/or law enforcement reports demonstrate that these types of substances are being abused for their psychoactive properties and they cause harm (see DEA 3-Factor Analysis). Recreational effects reported by abusers of synthetic cathinones include: Euphoria, sense of well-being, increased sociability, energy, empathy, increased alertness, improved concentration and focus. Adverse effects such as tachycardia, hypertension, rhabdomyolysis, hyponatremia, seizures, and altered mental status (paranoia, hallucinations, and delusions) have also been reported from the abuse of synthetic cathinones. Consequently, there are documented reports of emergency room admissions and deaths associated with the abuse of synthetic cathinone substances. With several generations of synthetic cathinones having been encountered since 2009, the abuse of *N*-ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, and 4-chloro-α-PVP is impacting or will negatively impact communities.

Law enforcement data indicate that *N*-ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, and 4-chloro-α-PVP have appeared in the United States' illicit drug market (see DEA 3-Factor Analysis). Law enforcement encounters include those reported to the National Forensic Laboratory Information System (NFLIS), a DEA sponsored program that systematically collects drug identification results and associated information from drug cases analyzed by Federal, State, and local forensic laboratories. From January 2012 to September 24, 2018, NFLIS registered 1,131 drug exhibits pertaining to the trafficking, distribution and abuse of *N*-ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, and 4-chloro-α-PVP. These exhibits had a net weight of approximately 18.7 kilograms \3\ and were encountered in powder, crystal, rock, resin, capsule and tablet forms.

\3\ Not all exhibits had weights recorded in the NFLIS database.

As observed by the DEA and by the United States Customs and Border Protection (CBP), synthetic cathinones originate from foreign sources, such as China. Bulk powder substances are smuggled via common carrier into the United States and find their way to clandestine designer drug product manufacturing operations located in residential neighborhoods, garages, warehouses, and other similar destinations throughout the country. There have been encounters of *N*-ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, and 4-chloro-α-PVP by the CBP (see DEA 3-Factor Analysis).

N-Ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, and 4-chloro-α-PVP have no accepted medical use in the United States. *N*-Ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, and 4-chloro-α-PVP have been seized by law enforcement in the United States. The misuse of α-PHP, 4–MEAP, MPHP, and PV8 has been reported to result in adverse effects in humans in the United States. Although no overdose information is currently available for *N*-ethylhexedrone and 4-chloro-α-PVP, law enforcement seizures of these two substances and their pharmacological similarity to currently controlled schedule I synthetic cathinones (e.g., methcathinone, mephedrone, methylone, pentylone, MDPV) suggest that these two synthetic cathinones are likely to produce adverse effects similar to those produced by other synthetic cathinones.

N-Ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, and 4-chloro-α-PVP are synthetic cathinones that have pharmacological effects similar to schedule I synthetic cathinone substances such as methcathinone, mephedrone, methylone, pentylone, and MDPV and schedule II stimulants such as methamphetamine and cocaine. The misuse of α-PHP, 4–MEAP, MPHP, and PV8 has been associated with one or more overdoses with some requiring emergency medical intervention in the United States. With no approved medical use and limited safety or toxicological information, *N*-ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, and 4-chloro-α-PVP have emerged on the designer drug market, and the abuse or trafficking of these substances for their psychoactive properties is concerning.

Factor 4. History and Current Pattern of Abuse

N-Ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, and 4-chloro-α-PVP are synthetic cathinones that have been identified in the United States' illicit drug market. Evidence indicates that these substances are being substituted for schedule I synthetic cathinones. Products containing synthetic cathinones have been falsely marketed as "research chemicals," "jewelry cleaner," "stain remover," "plant food or fertilizer," "insect repellants," or "bath salts." They have been sold at smoke shops, head shops, convenience stores, adult bookstores, and gas stations. They can also be purchased on the internet. These substances are commonly encountered in the form of powders, crystals, tablets, and capsules. Other encountered forms include resin, rock, liquid, and deposits on plant matter. Law enforcement has encountered *N*-ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, and 4-chloro-α-PVP in powder, crystal, resin, rock, capsule, or tablet forms. The packages of these commercial products usually contain the warning "not for human consumption," most likely in an effort to circumvent statutory restrictions for these substances.

N-Ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, and 4-chloro-α-PVP are likely to be abused in the same manner as schedule I synthetic cathinones such as methcathinone, mephedrone, methylone, pentylone, and MDPV. Information from published scientific studies indicate that the most common routes of administration for synthetic cathinones are nasal insufflation by snorting the powder and ingestion by swallowing capsules or tablets. The powder can also be injected or swallowed. Other methods of intake include rectal administration, ingestion by "bombing" (wrapping a dose of powder in a paper wrap and swallowing) and intramuscular injection.

Based upon the information collected from case reports, medical journals, and scientific publications including survey data, the main users of synthetic cathinones are youths and young adults. Given that *N*-ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, and 4-chloro-α-PVP are newly emerging synthetic cathinones, it is likely that these substances will be used by the same population. This is consistent with data collected from the use of schedule I synthetic cathinones (e.g., mephedrone, methylone, pentylone, MDPV). According to Monitoring the Future (MTF) survey data,\4\ the 2017 annual prevalence rate of synthetic cathinone use was 0.6% for high school seniors and 0.3% for young adults (19--30 years). However, there was an 18 percentage point increase in the perceived risk of trying "bath salts" in young adults (aged 19--26 years).

\4\ Monitoring the Future (MTF) is a research program conducted at the University of Michigan's Institute for Social Research under grants from NIDA. MTF tracks drug use trends among United States adolescents in the 8th, 10th, and 12th grades and high school graduates into adulthood by conducting national surveys.

N-Ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, and 4-chloro-α-PVP are likely to have duration of effects similar to those of schedule I synthetic cathinones because of their structural and pharmacological similarities. Users report (drug surveys, scientific and medical literature, etc.) that the effects of synthetic cathinones occur a few

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minutes to 15 minutes after administration, depending on the synthetic cathinone and the route of administration (oral, insufflation, intravenous, etc.), and can last up to three hours.

Evidence indicated that *N*-ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, and 4-chloro-α-PVP are ingested with other substances. This is likely to either heighten the effects or ameliorate the come-down effects of the synthetic cathinones. Co-ingestions can be from the ingestion of multiple products separately or a single product that is composed of multiple substances (e.g., one tablet containing *N*-ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, 4-chloro-α-PVP, and other illicit substances). Indeed, law enforcement routinely encounters synthetic cathinone mixtures. Substances found in combination with *N*-ethylhexedrone, α-PHP, 4–MEAP, MPHP, PV8, or 4-chloro-α-PVP are: Other synthetic cathinones (e.g., MDPV, 4-chloromethcathinone, N-ethylpentylone, α-PVP), common cutting agents (e.g., caffeine), or other substances of abuse (e.g., methamphetamine, fentanyl, fentanyl analogues, carfentanil, benzodiazepines (e.g., alprazolam), heroin, cocaine, synthetic cannabinoids, fluoroamphetamine, MDMA). Multiple drug use and potential co-ingestions are confirmed by forensic analysis of seized and purchased synthetic cathinone products.

Factor 5. Scope, Duration and Significance of Abuse

Since 2009, the popularity of synthetic cathinones and their associated products has continued, as evidenced by law enforcement seizures, public health information, and media reports. As one synthetic cathinone is controlled, another unscheduled synthetic cathinone appears in the recreational drug market. *N*-Ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP are synthetic cathinones that have been identified in the United States' illicit drug market (see DEA 3-Factor Analysis for a full discussion).

Law enforcement data indicate that *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP are being abused in the United States as recreational drugs. While law enforcement data are not direct evidence of abuse, the data can infer that a drug has been diverted and abused.\5\ Forensic laboratories have confirmed the presence of these substances in drug exhibits received from state, local, and federal law enforcement agencies. From January 2012 to September 24, 2018, there were 1,131 exhibits reported to NFLIS databases (Federal, State and local forensic laboratories) pertaining to the trafficking, distribution and abuse of *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP. These exhibits had a net weight of approximately 18.7 kilograms.\6\ These data also indicated that the abuse of *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP is widespread and has been encountered in many states since 2012 in the United States.

\5\ See 76 FR 77330, 77332, Dec. 12, 2011.

\6\ Not all exhibits had weights recorded in the NFLIS database.

The following information details data obtained from the NFLIS database (queried on September 24, 2018), including dates of first encounter, exhibits/reports, and locations.

N-Ethylhexedrone: NFLIS—233 reports, first encountered in August 2016, locations include: Arizona, Florida, Georgia, Illinois, Indiana, Kansas, Kentucky, Louisiana, Michigan, Minnesota, Mississippi, Missouri, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, South Carolina, Tennessee, Texas, Virginia, and Wyoming.

α-PHP: NFLIS—395 reports, first encountered in May 2014, locations include: Arkansas, California, Colorado, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kentucky, Maine, Massachusetts, Michigan, Minnesota, Missouri, New Hampshire, New Jersey, New York, Ohio, Oregon, Pennsylvania, South Carolina, South Dakota, Tennessee, Texas, Utah, Virginia, Wisconsin, and Wyoming.

4-MEAP: NFLIS—105 reports, first encountered in August 2013, locations include: Alabama, Arkansas, California, Colorado, Connecticut, Florida, Georgia, Illinois, Indiana, Kansas, Louisiana, Maryland, Minnesota, New Hampshire, New York, Ohio, Oklahoma, Oregon, Pennsylvania, Tennessee, and Texas.

MPHP: NFLIS—71 reports, first encountered in June 2012, locations include: California, Connecticut, Florida, Georgia, Indiana, Kansas, Kentucky, Maine, Minnesota, Missouri, Nebraska, Nevada, New Jersey, Ohio, Pennsylvania, and Texas.

PV8: NFLIS—166 reports, first encountered in December 2013, locations include: Arizona, Connecticut, District of Columbia, Florida, Georgia, Idaho, Indiana, Iowa, Kentucky, Louisiana, Maine, Massachusetts, Minnesota, Missouri, Nebraska, Nevada, New Hampshire, New Jersey, New York, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, South Carolina, Tennessee, Texas, Utah, Virginia, and Wisconsin.

4-Chloro-α-PVP: NFLIS—160 reports, first encountered in December 2015, locations include: California, District of Columbia, Louisiana, Maryland, Arizona, Connecticut, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Maine, Massachusetts, Minnesota, Missouri, New Jersey, New York, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Utah, Virginia, and Washington.

Additionally, encounters/seizures of these substances have occurred by the CBP at United States ports of entry. As observed by the DEA and CBP, synthetic cathinones originate from foreign sources, such as China. Bulk powder substances are smuggled via common carrier into the United States and find their way to clandestine designer drug product manufacturing operations located in residential neighborhoods, garages, warehouses, and other similar destinations throughout the country. From 2014 to 2017, CBP encountered 73 shipments of products containing *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, or 4-chloro-α-PVP. Additional evidence indicates that some of these synthetic cathinones have been seized abroad. *N*-Ethylhexedrone and 4-chloro-α-PVP have been identified in seized materials in China and Poland, respectively. These data demonstrate that these substances are being trafficked and abused in the United States and abroad.

Concerns over the abuse of synthetic cathinone substances have led to the control of many synthetic cathinones. DEA controlled 13 synthetic cathinones: methylone, mephedrone, MDPV, 4-methyl-N-ethylcathinone (4-MEC), 4-methyl-*alpha*-pyrrolidinopropiophenone (4-MePPP), *alpha*-pyrrolidinopentiophenone (α-PVP), butylone (1-(1,3-benzodioxol-5-yl)-2-(methylamino)butan-1-one), pentedrone (2-(methylamino)-1-phenylpentan-1-one), pentylone, 4-fluoro-N-methylcathinone (4-FMC), 3-fluoro-N-methylcathinone (3-FMC), naphyrone (1-(naphthalen-2-yl)-2-(pyrrolidin-1-yl)pentan-1-one), and *alpha*-pyrrolidinobutiophenone (α-PBP) from 2011 to 2014 (October 21, 2011; 76 FR 65371 and March 7, 2014; 79 FR 12938). Recently, DEA controlled another synthetic cathinone, N-ethylpentylone (August, 31, 2018; 83 FR 44474), as a schedule I substance.

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Factor 6. What, if Any, Risk There Is to the Public Health

Available evidence on the overall public health risks associated with the use of synthetic cathinones suggests that *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP can cause acute health problems leading to emergency department (ED) admissions, violent behaviors causing harm to self or others, or death. Acute adverse effects of synthetic cathinone substances are those typical of sympathomimetic agents (e.g., cocaine, methamphetamine, amphetamine) and include among other effects tachycardia, headache, palpitations, agitation, anxiety, mydriasis, tremor, fever or sweating, and hypertension. Other effects, with possible public health risk implications, that have been reported from the use of synthetic cathinone substances include psychological effects such as psychosis, paranoia, hallucinations, and agitation.

α-PHP, 4-MEAP, MPHP, and PV8 have been associated with the overdoses or deaths of individuals. There have been documented reports of ED admissions or deaths associated with the abuse of α-PHP, 4-MEAP, MPHP, and PV8. Individuals under the influence of 4-MEAP and MPHP have acted violently or unpredictably causing harm, or even death, to themselves or others. Adverse effects associated with α-PHP, 4-MEAP, MPHP, and PV8 abuse included vomiting, agitation, paranoia, hypertension, unconsciousness, tachycardia, seizures, cardiac arrest, rhabdomyolysis, or death. No overdose information is currently available for *N*-ethylhexedrone and 4-chloro-α-PVP, but the pharmacological similarity of these substances to other currently controlled schedule I synthetic cathinones (e.g., methcathinone, mephedrone, methylone, pentylone, MDPV) suggests that these substances can also pose an imminent hazard to public safety.

It remains highly likely that additional cases of adverse health effects involving α-PHP, 4-MEAP, MPHP, and PV8 in the United States may have occurred and will continue to be under-reported as these substances, as well as *N*-ethylhexedrone and 4-chloro-α-PVP, are not part of standard panels for biological specimens. The pharmacological data for *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP alone or combined with documented case reports, if any, demonstrate that the potential for fatal and non-fatal overdoses exists for *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP; thus, these substances pose an imminent hazard to the public health and safety.

As found with other synthetic cathinone substances, products containing synthetic cathinones often do not bear labeling information regarding the ingredients or the health risks and potential hazards associated with these products. The limited knowledge about product content and its purity, as well as lack of information about its effects, pose additional risks for significant adverse health effects to the users.

Based on pharmacological data or documented case reports of overdose fatalities, the misuse and abuse of *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP leads to the same qualitative public health risks as schedule I and II substances such as cathinone, methcathinone, mephedrone, methylone, pentylone, MDPV, methamphetamine, cocaine, and MDMA. α-PHP, MPHP, and PV8 have been associated with fatalities. As the data demonstrates, the potential for fatal and non-fatal overdoses exists for *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP; thus, *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP pose an imminent hazard to the public safety.

N-Ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP are being encountered on the illicit drug market in the United States and have no accepted medical use in the United States. Regardless, these products continue to be easily available and abused by diverse populations.

Finding of Necessity of Schedule I Placement To Avoid Imminent Hazard to Public Safety

In accordance with **21 U.S.C. 811**(h)(3), based on the available data and information summarized above, the continued uncontrolled manufacture, distribution, reverse distribution, importation, exportation, conduct of research and chemical analysis, possession, and/or abuse of *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP, resulting from the lack of control of these substances, pose an imminent hazard to the public safety. The DEA is not aware of any currently accepted medical uses for *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP in the United States. A substance meeting the statutory requirements for temporary scheduling, 21 U.S.C. 811(h)(1), may only be placed in schedule I. 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. Available data and information for *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP indicate that these synthetic cathinones 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. As required by section 201(h)(4) of the CSA, 21 U.S.C. 811(h)(4), the Acting Administrator, through a letter dated March 9, 2018, notified the Assistant Secretary of the DEA's intention to temporarily place *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP in schedule I. DEA published a notice of intent in the Federal Register on May 1, 2019. 84 FR 18423.

Conclusion

In accordance with the provisions of section 201(h) of the CSA, **21 U.S.C. 811**(h), the Acting Administrator considered available data and information, and herein sets forth the grounds for his determination to temporarily schedule *N*-ethylhexedrone (2-(ethylamino)-1-phenylhexan-1-one); *alpha*-pyrrolidinohexanophenone (1-phenyl-2-(pyrrolidin-1-yl)hexan-1-one; *alpha*-pyrrolidinohexiophenone; trivial name: α-PHP); 4-methyl-*alpha*-ethylaminopentiophenone (trivial name: 4-MEAP); 4'-methyl-*alpha*-pyrrolidinohexiophenone (1-(4-methylphenyl)-2-(pyrrolidin-1-yl)hexan-1-one; 4'-methyl-*alpha*-pyrrolidinohexanophenone; trivial name: MPHP); *alpha*-pyrrolidinoheptaphenone (1-phenyl-2-(pyrrolidin-1-yl)heptan-1-one; trivial name: PV8); and 4'-chloro-*alpha*-pyrrolidinovalerophenone (1-(4-chlorophenyl)-2-

(pyrrolidin-1-yl)pentan-1-one; 4'-chloro-*alpha*-pyrrolidinopentiophenone; trivial name: 4-chloro-α-PVP) in schedule I of the CSA, and finds that placement of *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP in schedule I of the CSA is necessary to avoid an imminent hazard to the public safety.

Because the Acting Administrator hereby finds that it is necessary to temporarily place *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP in schedule I to avoid an imminent hazard to the public safety, this temporary order scheduling these substances is effective on the date of publication in the Federal Register, and is in effect for a period of two years, with a possible extension of one additional year, pending completion of

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the regular (permanent) scheduling process. **21 U.S.C. 811**(h)(1) and (2).

The CSA sets forth specific criteria for scheduling a drug or other substance. Permanent scheduling actions in accordance with **21 U.S.C. 811**(a) are subject to formal rulemaking procedures done "on the record after opportunity for a hearing" conducted pursuant to the provisions of 5 U.S.C. 556 and 557. 21 U.S.C. 811. The permanent scheduling process of formal rulemaking affords interested parties with appropriate process and the government with any additional relevant information needed to make a determination. Final decisions that conclude the permanent scheduling process of formal rulemaking are subject to judicial review. **21 U.S.C. 877**. Temporary scheduling orders are not subject to judicial review. 21 U.S.C. 811(h)(6).

Requirements for Handling

Upon the effective date of this temporary order, *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP will be subject to the regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, reverse distribution, importation, exportation, engagement in research, and conduct of instructional activities or chemical analysis with, and possession of schedule I controlled substances including the following:

1. *Registration.* Any person who handles (manufactures, distributes, reverse distributes, imports, exports, engages in research, or conducts instructional activities or chemical analysis with, or possesses), or who desires to handle, *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP must be registered with the DEA to conduct such activities pursuant to **21 U.S.C. 822, 823, 957**, and **958**, and in accordance with **21 CFR parts 1301** and **1312**, as of July 18, 2019. Any person who currently handles *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP, and is not registered with the DEA, must submit an application for registration and may not continue to handle *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP as of July 18, 2019, unless the DEA has approved that application for registration pursuant to 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312. Retail sales of schedule I controlled substances to the general public are not allowed under the CSA. Possession of any quantity of these substances in a manner not authorized by the CSA on or after July 18, 2019 is unlawful and those in possession of any quantity of these substances may be subject to prosecution pursuant to the CSA.

2. *Disposal of stocks.* Any person who does not desire or is not able to obtain a schedule I registration to handle *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP must surrender all currently held quantities of *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP.

3. *Security. N*-Ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP are subject to schedule I security requirements and must be handled and stored in accordance with **21 CFR 1301.71-1301.93**, as of July 18, 2019.

4. *Labeling and Packaging.* All labels, labeling, and packaging for commercial containers of *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP must comply with **21 U.S.C. 825** and **958**(e) and be in accordance with **21 CFR part 1302**. Current DEA registrants shall have 30 calendar days from July 18, 2019, to comply with all labeling and packaging requirements.

5. *Inventory.* Every DEA registrant who possesses any quantity of *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP on the effective date of this order must take an inventory of all stocks of these substances on hand, pursuant to **21 U.S.C. 827** and **958**, and in accordance with **21 CFR 1304.03, 1304.04**, and **1304.11**. Current DEA registrants shall have 30 calendar days from the effective date of this order to be in compliance with all inventory requirements. After the initial inventory, every DEA registrant must take an inventory of all controlled substances (including *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP) on hand on a biennial basis, pursuant to 21 U.S.C. 827 and 958, and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11.

6. *Records.* All DEA registrants must maintain records with respect to *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP pursuant to **21 U.S.C. 827** and **958**(e), and in accordance with **21 CFR parts 1304, 1312, 1317** and **Sec. 1307.11**. Current DEA registrants authorized to handle *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP shall have 30 calendar days from the effective date of this order to be in compliance with all recordkeeping requirements.

7. *Reports.* All DEA registrants who manufacture or distribute *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP must submit reports pursuant to **21 U.S.C. 827** and in accordance with **21 CFR 1304** and **1312** as of July 18, 2019.

8. *Order Forms.* All DEA registrants who distribute *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP must comply with order form requirements pursuant to **21 U.S.C. 828** and in accordance with **21 CFR part 1305** as of July 18, 2019.

9. *Importation and Exportation.* All importation and exportation of *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP must be in compliance with **21 U.S.C. 952, 953, 957, 958**, and in accordance with **21 CFR part 1312** as of July 18, 2019.

10. *Quota.* Only DEA registered manufacturers may manufacture *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, and 4-chloro-α-PVP in accordance with a quota assigned pursuant to **21 U.S.C. 826** and in accordance with **21 CFR part 1303** as of July 18, 2019.

11. *Liability.* Any activity involving *N*-ethylhexedrone, α-PHP, 4-MEAP, MPHP, PV8, or 4-chloro-α-PVP not authorized by, or in violation of the CSA, occurring as of July 18, 2019, is unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

Regulatory Matters

Section 201(h) of the CSA, **21 U.S.C. 811**(h), provides for a temporary scheduling action where such action is necessary to avoid an imminent hazard to the public safety. As provided in this subsection, the Attorney General may, by order, schedule a substance in schedule I on a temporary basis. Such an order may not be issued before the expiration of 30 days from (1) the publication of a notice in the Federal Register of the intention to issue such order and the grounds upon which such order is to be issued, and (2) the date that notice of the proposed temporary scheduling order is transmitted to the Assistant Secretary of HHS. 21 U.S.C. 811(h)(1).

Inasmuch as section 201(h) of the CSA directs that temporary scheduling actions be issued by order (as distinct from a rule) and sets forth the procedures by which such orders are to be issued, the DEA believes that the notice and comment requirements of section 553 of the Administrative Procedure Act (APA), 5 U.S.C. 553, which are applicable to rulemaking, do not apply to this scheduling order. The specific language chosen by Congress indicates an intention for the DEA to proceed through the issuance of an order instead of proceeding by rulemaking. Given that Congress specifically requires the Attorney

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General to follow rulemaking procedures for other kinds of scheduling actions, see section 201(a) of the CSA, **21 U.S.C. 811**(a), it is noteworthy that, in section 201(h), Congress authorized the issuance of temporary scheduling actions by order rather than by rule.

In the alternative, even assuming that this action might be subject to section 553 of the APA, the Acting Administrator finds that there is good cause to forgo the notice and comment requirements of section 553, as any further delays in the process for issuance of temporary scheduling orders would be impracticable and contrary to the public interest in view of the manifest urgency to avoid an imminent hazard to the public safety.

Further, the DEA believes that this temporary scheduling action is not a "rule" as defined by 5 U.S.C. 601(2), and, accordingly, is not subject to the requirements of the Regulatory Flexibility Act (RFA). The requirements for the preparation of an initial regulatory flexibility analysis in 5 U.S.C. 603(a) are not applicable where, as here, the DEA is not required by section 553 of the APA or any other law to publish a general notice of proposed rulemaking.

Additionally, this action is not a significant regulatory action as defined by Executive Order 12866 (Regulatory Planning and Review), section 3(f), and, accordingly, this action has not been reviewed by the Office of Management and Budget.

This action will not have substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government. Therefore, in accordance with Executive Order 13132 (Federalism), it is determined that this action does not have sufficient federalism implications to warrant the preparation of a Federalism Assessment.

As noted above, this action is an order, not a rule. Accordingly, the Congressional Review Act (CRA) is inapplicable, as it applies only to rules. However, if this were a rule, pursuant to the CRA, "any rule for which an agency for good cause finds that notice and public procedure thereon are impracticable, unnecessary, or contrary to the public interest, shall take effect at such time as the federal agency promulgating the rule determines." 5 U.S.C. 808(2). It is in the public interest to schedule these substances immediately to avoid an imminent hazard to the public safety. This temporary scheduling action is taken pursuant to **21 U.S.C. 811**(h), which is specifically designed to enable the DEA to act in an expeditious manner to avoid an imminent hazard to the public safety. 21 U.S.C. 811(h) exempts the temporary scheduling order from standard notice and comment rulemaking procedures to ensure that the process moves swiftly. For the same reasons that underlie 21 U.S.C. 811(h), that is, the DEA's need to move quickly to place these substances in schedule I because they pose an imminent hazard to the public safety, it would be contrary to the public interest to delay implementation of the temporary scheduling order. Therefore, this order shall take effect immediately upon its publication. The DEA has submitted a copy of this temporary order to both Houses of Congress and to the Comptroller General, although such filing is not required under the Small Business Regulatory Enforcement Fairness Act of 1996 (Congressional Review Act), 5 U.S.C. 801-808 because, as noted above, this action is an order, not a rule.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, the DEA amends 21 CFR part 1308 as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

- 1. The authority citation for part 1308 continues to read as follows:

  Authority: 21 U.S.C. 811, 812, 871(b), **956**(b), unless otherwise noted.

- 2. In **Sec. 1308.11**, add paragraphs (h)(42) through (47) to read as follows:

Sec. 1308.11 Schedule I.

* * * * *

(h) * * *

(42) *N*-Ethylhexedrone, its optical, positional, and geometric isomers, salts and salts of isomers (Other name: 2-(ethylamino)-1-phenylhexan-1-one)	7246
(43) *alpha*-Pyrrolidinohexanophenone, its optical, positional, and geometric isomers, salts and salts of isomers (Other names: α-PHP; *alpha*-pyrrolidinohexiophenone; 1-phenyl-2-(pyrrolidin-1-yl)hexan-1-one)	7544
(44) 4-Methyl-*alpha*-ethylaminopentiophenone, its optical, positional, and geometric isomers, salts and salts of isomers (Other names: 4–MEAP; 2-(ethylamino)-1-(4-methylphenyl)pentan-1-one)	7245
(45) 4'-Methyl-*alpha*-pyrrolidinohexiophenone, its optical, positional, and geometric isomers, salts and salts of isomers (Other names: MPHP; 4'-methyl-*alpha*-pyrrolidinohexanophenone; 1-(4-methylphenyl)-2-(pyrrolidin-1-yl)hexan-1-one)	7446
(46) *alpha*-Pyrrolidinoheptaphenone, its optical, positional, and geometric isomers, salts and salts of isomers (Other names: PV8; 1-phenyl-2-(pyrrolidin-1-yl)heptan-1-one)	7548
(47) 4'-Chloro-*alpha*-pyrrolidinovalerophenone, its optical, positional, and geometric isomers, salts and salts of isomers (Other names: 4-chloro-α-PVP; 4'-chloro-*alpha*-pyrrolidinopentiophenone; 1-(4-chlorophenyl)-2-(pyrrolidin-1-yl)pentan-1-one)	7443

Dated: July 10, 2019.

Uttam Dhillon,
Acting Administrator.

[FR Doc. 2019-15184 Filed 7-17-19; 8:45 am]

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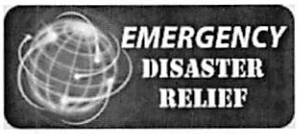

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Rules - 2020

[Federal Register Volume 85, Number 95 (Friday, May 15, 2020)]
[Proposed Rules]
[Pages 29359-29366]
From the Federal Register Online via the Government Publishing Office [www.gpo.gov]
[FR Doc No: 2020-09599]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-509]

Schedules of Controlled Substances: Placement of *para*-Methoxymethamphetamine (PMMA) in Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Drug Enforcement Administration proposes placing 1-(4-methoxyphenyl)-*N*-methylpropan-2-amine (*para*-

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methoxymethamphetamine, PMMA), including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible, in schedule I of the Controlled Substances Act. This action is being taken to enable the United States to meet its obligations under the 1971 Convention on Psychotropic Substances. If finalized, this action would impose the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances on persons who handle (manufacture, distribute, import, export, engage in research, conduct instructional activities or chemical analysis, or possess), or propose to handle PMMA.

DATES: Comments must be submitted electronically or postmarked on or before June 15, 2020.

Interested persons may file a request for hearing or waiver of hearing pursuant to **21 CFR 1308.44** and in accordance with **21 CFR 1316.45** and/or **1316.47**, as applicable. Requests for hearing and waivers of an opportunity for a hearing or to participate in a hearing must be received on or before June 15, 2020.

ADDRESSES: Interested persons may file written comments on this proposal in accordance with **21 CFR 1308.43**(g). Commenters should be aware that the electronic Federal Docket Management System will not accept comments after 11:59 p.m. Eastern Time on the last day of the comment period. To ensure proper handling of comments, please reference "Docket No. DEA-509" on all electronic and written correspondence, including any attachments.

- *Electronic comments:* DEA encourages that all comments be submitted electronically through the Federal eRulemaking Portal, which provides the ability to type short comments directly into the comment field on the web page or to attach a file for lengthier comments. Please go to http://www.regulations.gov and follow the online instructions at that site for submitting comments. Upon completion of your submission, you will receive a Comment Tracking Number for your comment. Please be aware that submitted comments are not instantaneously available for public view on Regulations.gov. If you have received a Comment Tracking Number, your comment has been successfully submitted and there is no need to resubmit the same comment.
- *Paper comments:* Paper comments that duplicate the electronic submission are not necessary. Should you wish to mail a paper comment in lieu of an electronic comment, it should be sent via regular or express mail to: Drug Enforcement Administration, Attn: DEA Federal Register Representative/DRW, 8701 Morrissette Drive, Springfield, Virginia 22152.
- *Hearing requests:* All requests for hearing and waivers of participation must be sent to: Drug Enforcement Administration, Attn: Administrator, 8701 Morrissette Drive, Springfield, Virginia 22152. All requests for hearing and waivers of participation should be sent to: Drug Enforcement Administration, Attn: Hearing Clerk/LJ, 8701 Morrissette Drive, Springfield, Virginia 22152; and (2) Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrissette Drive, Springfield, Virginia 22152.

FOR FURTHER INFORMATION CONTACT: Scott A. Brinks, Regulatory Drafting and Policy Support Section, Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (571) 362-8209.

SUPPLEMENTARY INFORMATION:

Posting of Public Comments

Please note that all comments received in response to this docket are considered part of the public record. They will, unless reasonable cause is given, be made available by the Drug Enforcement Administration (DEA) for public inspection online at http://www.regulations.gov. Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter. The Freedom of Information Act applies to all comments received. If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want it to be made publicly available, you must include the phrase "PERSONAL IDENTIFYING INFORMATION" in the first paragraph of your comment. You must also place all of the personal identifying information you do not want made publicly available in the first paragraph of your comment and identify what information you want redacted.

If you want to submit confidential business information as part of your comment, but do not want it to be made publicly available, you must include the phrase "CONFIDENTIAL BUSINESS INFORMATION" in the first paragraph of your comment. You must also prominently identify confidential business information to be redacted within the comment.

Comments containing personal identifying information and confidential business information identified as directed above will be made publicly available in redacted form. If a comment has so much confidential business information or personal identifying information that it cannot be effectively redacted, all or part of that comment may not be made publicly available. Comments posted to http://www.regulations.gov may include any personal identifying information (such as name, address, and phone number) included in the text of your electronic submission that is not identified as directed above as confidential.

An electronic copy of this document and supplemental information to this proposed rule are available at http://www.regulations.gov for easy reference.

Request for Hearing or Waiver of Participation in a Hearing

Pursuant to **21 U.S.C. 811**(a), this action is a formal rulemaking "on the record after opportunity for a hearing." Such proceedings are conducted pursuant to the provisions of the Administrative Procedure Act (APA), 5 U.S.C. 551-559. **21 CFR 1308.41-1308.45; 21 CFR part 1316**, subpart D. Such requests or notices must conform to the requirements of **21 CFR 1308.44**(a) or (b), and **1316.47** or **1316.48**, as applicable, and include a statement of the person's interests in the proceeding and the objections or issues, if any, concerning which the person desires to be heard. Any waiver must conform to the requirements of 21 CFR 1308.44(c) and may include a written statement regarding the interested person's position on the matters of fact and law involved in any hearing.

All requests for hearing and waivers of participation must be sent to DEA using the address information provided above.

Legal Authority

The United States is a party to the 1971 United Nations Convention on Psychotropic Substances (1971 Convention), February 21, 1971, 32 U.S.T. 543 as amended. Procedures respecting changes in drug schedules under the 1971 Convention are governed domestically by **21 U.S.C. 811**(d)(2-4). When the United States receives notification of a scheduling decision pursuant to Article 2 of the 1971 Convention adding a drug or other substance to a specific schedule, the Secretary of the Department of Health and Human Services (HHS),\1\ after

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consultation with the Attorney General, shall first determine whether existing legal controls under subchapter I of the Controlled Substances Act (CSA) and the Federal Food, Drug, and Cosmetic Act meet the requirements of the schedule specified in the notification with respect to the specific drug or substance. **21 U.S.C. 811**(d)(3). If such requirements are not met by existing controls and the Secretary of HHS concurs in the scheduling decision, the Secretary shall recommend to the Attorney General that he initiate proceedings for scheduling the drug or substance under the appropriate schedule pursuant to 21 U.S.C. 811(a) and (b). 21 U.S.C. 811(d)(3)(B).

\1\ As discussed in a memorandum of understanding entered into by the Food and Drug Administration (FDA) and the National Institute on Drug Abuse (NIDA), FDA acts as the lead agency within HHS in carrying out the Secretary's scheduling responsibilities under the CSA, with the concurrence of NIDA. 50 FR 9518, March 8, 1985. The Secretary of HHS has delegated to the Assistant Secretary for Health of HHS the authority to make domestic drug scheduling recommendations. 58 FR 35460, July 1, 1993.

In the event that the Secretary of HHS did not consult with the Attorney General, as provided under **21 U.S.C. 811**(d)(3), and the Attorney General did not issue a temporary order, as provided under 21 U.S.C. 811(d)(4), the procedures for permanent scheduling set forth in 21 U.S.C. 811(a) and (b) control. Pursuant to 21 U.S.C. 811(a)(1), the Attorney General may, by rule, add to such a schedule or transfer between such schedules any drug or other substance, if he finds that such drug or other substance has a potential for abuse, and makes with respect to such drug or other substance the findings prescribed by **21 U.S.C. 812**(b) for the schedule in which such drug or other substance is to be placed. The Attorney General has delegated this scheduling authority to the Administrator of DEA (Administrator). 28 CFR 0.100.

Background

para-Methoxymethamphetamine (PMMA) is a substituted phenethylamine and shares structural similarity to methamphetamine (schedule II) and *para*-methoxyamphetamine (PMA), schedule I. PMMA shares a similar pharmacological profile with 3,4-methylenedioxymethamphetamine (MDMA or ecstasy), a schedule I substance with high potential for abuse. Similar to MDMA, data obtained from preclinical studies show that PMMA's effects are mediated by monoaminergic (dopamine, norepinephrine, and serotonin) transmission, mostly via activation of the serotonergic system. In animals, PMMA mimics MDMA in producing discriminative stimulus effect, indicative of similar subjective effects. Law enforcement has encountered PMMA on the recreational drug market. In this market, PMMA is available and sold as "ecstasy" either alone or in combination with MDMA or PMA for oral consumption. For many years, there has been worldwide (mostly in Europe) reporting of non-fatal and fatal cases of overdoses involving PMMA. PMMA has no accepted medical use in treatment in the United States.

Proposed Determination To Schedule PMMA

On March 18, 2016, the Commission on Narcotic Drugs (CND) voted to place PMMA in Schedule I of the 1971 Convention (CND Dec/59/3) during its 59th Session due to its dependence and abuse potential. The United States is a member of the 1971 Convention, and in accordance with **21 U.S.C. 811**(b), on April 7, 2017, DEA, after gathering the necessary data, requested from HHS \2\ a scientific and medical evaluation and a scheduling recommendation for PMMA. On December 18, 2018, pursuant to 21 U.S.C. 811(b), HHS provided DEA with a scheduling recommendation entitled "Basis for the Recommendation to Place 1-(4-methoxyphenyl)-*N*-methylpropan-2-amine (*para*-methoxymethamphetamine, PMMA) in Schedule I of the Controlled Substances Act."

\2\ Administrative responsibilities for evaluating a substance for control under the CSA are performed for HHS by FDA, with the concurrence of NIDA, according to a Memorandum of Understanding. 50 FR 9518, March 8, 1985.

Upon receipt of the scientific and medical evaluation and scheduling recommendation from HHS, DEA reviewed the documents and all other relevant data, and conducted its own 8-Factor analysis in accordance with **21 U.S.C. 811**(c). Included below is a brief summary of each factor as analyzed by HHS and DEA, and as considered by DEA in the scheduling decision. Please note that both DEA and HHS 8-Factor analyses are available in their entirety under the tab "Supporting Documents" of the public docket for this action at http://www.regulations.gov under Docket Number "DEA-509."

1. *The Drug's Actual or Relative Potential for Abuse:* The term "abuse" is not defined in the CSA. However, the legislative history of the CSA suggests that DEA consider the following criteria when determining whether a particular drug or substance has a potential for abuse: \3\

\3\ Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970); reprinted in 1970 U.S.C.C.A.N. 4566, 4603.

(a) There is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community; or

(b) There is significant diversion of the drug or drugs containing such a substance from legitimate drug channels; or

(c) Individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice; or

(d) The drug or drugs containing such a substance are new drugs so related in their action to a drug or drugs already listed as having a potential for abuse to make it likely that the drug will have the same potentiality for abuse as such drugs, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.

According to HHS, there is currently no approved medical use in treatment for PMMA anywhere in the world, and there is no Food and Drug Administration (FDA)-approved drug product containing PMMA used in treatment in the United States. Evidence demonstrates that PMMA, similar to MDMA, is abused for its stimulant, psychedelic, and empathogenic effects. Over a period of approximately 30 years starting in the 1990s, PMMA has been associated with numerous cases of non-fatal intoxications (n = 31) and fatal intoxications (n = 131) in three continents. PMMA and its metabolites have been positively identified in blood, urine, and hair samples of individuals with a substance use disorder. Evidence posits that PMMA is abused knowingly and/or unknowingly as an MDMA (ecstasy) substitute.

Law enforcement seizure \4\ data indicate that individuals have abused and are continuing to abuse PMMA. According to the National Forensic Laboratory Information System (NFLIS) \5\ database, which collects drug identification results from drug cases

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submitted to and analyzed by some Federal, State, and local forensic laboratories, there have been 39 reports for PMMA between January 2002 and October 2019, and no reports for PMMA from January 2003 to December 2010, January 2013 to December 2013, and January 2017 to December 2017 (query date: October 23, 2019).\6\ The identification of this substance on the illicit drug market is an indication that individuals are taking PMMA in amounts sufficient to create a hazard to public health. In the United States, PMMA is not an approved drug product, and there appears to be no legitimate source for this substance as a marketed drug product.

\4\ While law enforcement data is not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. See 76 FR 77330, 77332, December 12, 2011.

\5\ NFLIS represents an important resource in monitoring illicit drug trafficking, including the diversion of legally manufactured pharmaceuticals into illegal markets. NFLIS-Drug is a comprehensive information system that includes data from forensic laboratories that handle the Nation's drug analysis cases. NFLIS-Drug participation rate, defined as the percentage of the national drug caseload represented by laboratories that have joined NFLIS, is currently 98.5%. NFLIS includes drug chemistry results from completed analyses only. While NFLIS data is not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. See 76 FR 77330, 77332, December 12, 2011. NFLIS data were queried October 23, 2019.

\6\ NFLIS is still reporting data for October-December 2018, due to normal lag time in reporting.

Based on available data, PMMA is related in its effects to the actions of other substances such as PMA (schedule I) and MDMA (schedule I) that are already listed as having potential for abuse. According to HHS, PMMA has similar pharmacological effects to MDMA, and thus is expected to have a high potential for abuse and high risk to public health.

2. *Scientific Evidence of the Drug's Pharmacological Effects, if Known:* According to HHS, PMMA is an empathogenic drug that produces mild stimulant and psychedelic effects. Data obtained from in vitro studies show that similar to MDMA, PMMA significantly increased dopamine (DA) and serotonin (5-HT) levels in brain regions associated with abuse liability. Data obtained from an enzymatic assay demonstrate that PMMA inhibited monoamine oxidase A and B. According to HHS, results from the enzymatic study may partially explain the higher levels of monoamines seen with PMMA administration in brain microdialysis studies. High levels of monoamines, especially 5-HT, can lead to a serious medical condition referred to as serotonin syndrome. High doses of PMMA have been associated with symptoms of serotonin syndrome, including increased body temperature (hyperthermia), tremor, and agitation, which can lead to death.

In preclinical studies, high doses of PMMA transiently increased locomotor activity. HHS stated that PMMA's locomotor stimulatory effects are not as robust as that of amphetamine or methamphetamine. In drug discrimination studies, using a test to determine physical or behavioral effects (an interoceptive response) of an unknown drug, the effects of PMMA are different from structural analogs, amphetamine or 2,5-dimethoxy-4-methylamphetamine (DOM). However, in rats trained to discriminate between MDMA or PMMA, MDMA and PMMA cross-substitute for one another. Based on these and additional data, HHS stated that PMMA likely has similar psychoactive effects as MDMA.

There are no clinical studies conducted with PMMA. However, according to HHS, an article described that a self-administered 110 milligram (mg) dose of PMMA resulted in compulsive yawning and increased pulse one hour post-administration. The described effects returned "back to baseline" four hours post-administration. A study examined the psychoactive effects of individuals who had taken "ecstasy." The study followed 5,786 individuals who provided the tablets for a chemical analysis and reported on their subjective effects. Out of this sample set, 70 (1.2 percent) "ecstasy" tablets were identified as containing PMMA and MDMA together, with PMMA concentrations in a range of 5.0 to 128.0 mg/tablet. It was noted that abusers of the PMMA and MDMA combination experienced hyperthermic seizures, palpitations, agitation, hallucinations, abdominal cramps, nausea, dizziness, and headache.

In summary, PMMA is a psychoactive substance with a mechanism of action similar to that of MDMA. Data from in vitro studies show that PMMA increases serotonin levels more than dopamine levels in the brain reward circuitry. In addition, PMMA has an inhibitory effect on monoamine oxidase-A enzyme that further increases monoamine levels and can lead to serotonin syndrome, a dangerous medical condition. Data from animal studies demonstrate that PMMA produced locomotor stimulant effects at high doses with potency of about six times less than that of (+)-amphetamine. In drug discrimination studies, PMMA produces stimulus effect similar to MDMA in rats. Both PMMA and MDMA cross-substitute for one another. There are currently no controlled clinical studies that have evaluated the effects of PMMA in humans. However, anecdotal reports show that similar to MDMA, PMMA produces adverse health effects, such as hyperthermia, seizures, hallucinations, and nausea. Taken together, these data demonstrate that PMMA shares a mechanism of action and discriminative stimulus effects similar to the schedule I substance, MDMA.

3. *The State of Current Scientific Knowledge Regarding the Drug or Other Substance:* PMMA is a substituted phenethylamine and is a methoxy-derivative of methamphetamine. PMMA is also related to PMA and MDMA, which are schedule I substances.

As stated by HHS, there are several sources describing the synthesis of PMMA either directly or through alternate route by conversion of PMA to PMMA. The precursor substances that can be used for the synthesis of PMMA include methylamine, 4-methoxyphenyacetone, and cyanoborohydride. Additional chemicals and solvents required for PMMA synthesis include methanol, dichloromethane, isopropanol, hydrochloric acid, ethyl chloroformate, trimethylamine, carbamate, formamide, and lithium aluminum hydride.

Pharmacokinetic studies of PMMA in rats showed that after subcutaneous administration, peak PMMA concentration was detected in the plasma within 30 minutes. Brain levels of PMMA were delayed behind the plasma levels for several hours. HHS states that this delay supports user comments that PMMA has a longer onset of effect than MDMA. Most of PMMA and its metabolites were excreted within the first 24-hours post-administration. Metabolites detected were products of *O*-demethylation or N-demethylation of PMMA to 4-methoxyamphetamine (PMA), 4-hydroxymethamphetamine (OH-MAM), 4-hydroxyamphetamine (OH-AM), 4-hydroxy-3'-methoxymethamphetamine (HM-MAM), and 4'-hydroxy-3'-methoxyamphetamine (HM-AM). The cytochrome P450 enzyme CYP2D6 was identified as being the only enzyme capable of demethylating PMMA.

PMMA toxicity data in animals demonstrate that toxicity occurs at early stages of administration. In PMMA-dosed animals, prior to lethality, hyperactivity, increased respiration, salivation, and tremor were observed.

4. *Its History and Current Pattern of Abuse:* Abuse of PMMA was first documented in the late 1980s and associated with "ecstasy" tablets as this drug was often substituted for MDMA. Abuse of PMMA has been documented worldwide with usage particularly extensive in Europe, Asia, and Canada. PMMA was originally used as a powder with doses ranging around 100 mg or less. PMMA is now most commonly encountered in a tablet form, and PMMA tablets have been seized in Europe, Asia, and the United States.

PMMA tablets are primarily sold as "ecstasy" and are sometimes encountered along with amphetamine, methamphetamine, or ephedrine. PMMA tablets may be marked with different logos, including "E," "Mitsubishi," "Jumbo," or "Superman." Street names for PMMA tablets include "Dr. Death," "Death," or "Killer." According to a review of PMMA by the

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European Monitoring Centre for Drugs and Drug Addition (EMCDDA) in 2003, tablets were reported to contain between 20 and 97 mg of PMMA. PMMA is primarily administered orally in a tablet form. Data indicate that MDMA is often mixed with other substances, one of which is PMMA. It was observed that MDMA mixed with PMMA led to a higher number of adverse events than other MDMA combinations. According to HHS, there is little anecdotal information on the use of PMMA most likely because individuals ingesting this substance in the context of abuse believe they are taking MDMA rather than a mixture of drugs that may include PMMA thus attributing its effects to MDMA.

DEA conducted a search of NFLIS and the System to Retrieve Information from Drug Evidence (STRIDE)/STARLIMS for law enforcement encounters of PMMA. Prior to October 1, 2014, STRIDE collected the analytical results of drug evidence submitted by DEA, other Federal law enforcement agencies, and some local law enforcement agencies to DEA forensic laboratories. Since October 1, 2014, STARLIMS (a web-based, commercial laboratory information management system) has replaced STRIDE as DEA laboratory drug evidence data system of record. DEA laboratory data submitted after September 30, 2014, are reposited in STARLIMS. According to data from STRIDE \7\ and STARLIMS \8\ between January 2000 and December 2018, DEA laboratories analyzed 41 drug exhibits containing PMMA. NFLIS is a DEA program that collects drug identification results from drug cases analyzed by other Federal, State, and local forensic laboratories. Within the NFLIS database, there have been 39 reports \9\ for PMMA between January 2002 and October 2019, and no reports from January 2003 to December 2010, January 2013 to December 2013, and January 2017 to December 2017 from state and local laboratories. The NFLIS database shows there were two reports in 2002 from one state; three reports from two states in 2011; three reports from three states in 2012; 21 reports from one state in 2014; three reports from two states in 2015; two reports from one state in 2016; four reports from two states in 2018; and one report from one state in 2019.

\7\ STRIDE data were queried through September 30, 2014, by the date of collection for DEA forensic laboratories.

\8\ STRIDE/STARLIMS was queried October 23, 2019, by the date of collection.

\9\ NFLIS is still reporting data for October-December 2018, due to normal lag time in reporting.

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5. *The Scope, Duration, and Significance of Abuse:* PMMA abuse has been associated with "ecstasy" tablets and is used as a substitute for MDMA. As a result, most users think they are taking "ecstasy" with MDMA and are not intentionally purchasing PMMA on the illicit market. One study reported that tablets containing a combination of MDMA and PMMA resulted in adverse effects, such as hyperthermic seizures, palpitations, agitation, nausea, and hallucinations. Most abusers of PMMA take the drug in combination with other drugs as noted in the PMMA-associated deaths (see Factor 6). Furthermore, there is evidence of PMMA drug seizures or confiscation in the United States, as reported by DEA's STRIDE/STARLIMS or NFLIS databases.

Numerous deaths and overdoses associated with PMMA usage demonstrate that there is a considerable population abusing PMMA, and its abuse is a significant public health concern. Prior to death, individuals exhibit high temperatures, seizures, coma, and respiratory distress. The PMMA-related public health risks, such as deaths and overdoses, led the European Union Member States to control PMMA in 2002.

6. *What, if Any, Risk There Is to the Public Health:* According to HHS, there are several risk factors associated with the use of PMMA. The first risk is that individuals inadvertently use PMMA because it is sold as MDMA and such products may contain other drugs. This risk can lead to poly-drug use, which is inherently more dangerous to the individuals who consume such products. The second risk described by HHS is the slow onset of action of PMMA compared to MDMA. The delay in onset of effect for PMMA can make individuals consume more PMMA, and such action can lead to overdose or death. Thirdly, HHS described that the pharmacological actions of PMMA, such as increase in monoamine levels (DA and 5-HT) combined with inhibition of monoamine oxidase-A, an enzyme responsible for degradation of these monoamines, can lead to a serious medical condition known as serotonin syndrome. The symptoms of serotonin syndrome are similar to those seen when high doses of PMMA are used. These include hyperthermia, tremor, agitation, and can result in death.

Over a period of approximately 30 years starting in the 1990s, a total of 131 analytically confirmed PMMA (detected in either blood and/or urine)-associated deaths in Europe (69 deaths), Israel (27 deaths), Canada (27 deaths), and Taiwan (8 deaths) has been reported. Published case reports on PMMA-related deaths occurred mostly in males and ages ranged from 14-59 years with the majority of them under the age of 30. Common symptoms that were observed prior to death were hyperthermia, decreased respiratory rate, seizures, and cardiac arrest. In most of the PMMA-related fatalities, other drugs were detected in the blood or urine.

7. *Its Psychic or Physiological Dependence Liability:* According to HHS, abuse liability of PMMA has only been characterized through drug discrimination studies. The drug discrimination studies do not provide information that can be used to assess the psychic or physiological dependence liability of PMMA, although they provide information on the subjective effects of the drug. Data from drug discrimination studies showed that both PMMA and MDMA share discriminative stimulus effects.

Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, indicated that there is evidence of a withdrawal syndrome from MDMA with observations of both psychological and physical dependence. Similarities in the drug discriminative stimulus properties of PMMA and MDMA indicate that the subjective effects of PMMA are similar to that of the schedule I substance, MDMA. As stated by HHS, both PMMA and MDMA also largely share a common mechanism of action. Thus, it is plausible to extrapolate that PMMA has a dependence liability similar to that of MDMA. HHS states some individuals have become tolerant to MDMA resulting in taking high doses of the drug, and these individuals have reported undergoing a withdrawal syndrome, although it is unclear whether they were undergoing withdrawal or adverse effects from high doses of MDMA. Thus, evidence suggests that MDMA causes psychological dependence and may be associated with physical dependence, although not to the same extent as that of cocaine.

HHS concludes that PMMA most likely has a psychic dependence liability similar to that of MDMA, though not as strong as that of cocaine. The use of PMMA may be associated with physical dependence.

8. *Whether the Substance is an Immediate Precursor of a Substance Already Controlled Under the CSA:* PMMA is not an immediate precursor to any substance already controlled in the CSA as defined by **21 U.S.C. 802(23).**

Conclusion: After considering the scientific and medical evaluation conducted by HHS, HHS's scheduling recommendation, and DEA's own 8-Factor analysis, DEA finds that the facts and all relevant data constitute substantial evidence of the potential for

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abuse of PMMA. As such, DEA hereby proposes to schedule PMMA as a schedule I controlled substance under the CSA.

Proposed Determination of Appropriate Schedule

The CSA establishes five schedules of controlled substances known as schedules I, II, III, IV, and V. The CSA also outlines the findings required to place a drug or other substance in any particular schedule. **21 U.S.C. 812(b).** After consideration of the analysis and recommendation of the Assistant Secretary for Health of HHS and review of all available data, the Acting Administrator of DEA, pursuant to **21 U.S.C. 811(c)** and 812(b)(1), finds the following:

(1) The Drug or Substance Has a High Potential for Abuse

PMMA has a mechanism of action similar to that of the schedule I substance MDMA. Similar to MDMA, PMMA increases levels of monoamines, specifically DA and 5-HT, in the brain reward circuitry. Data from animal studies demonstrate that PMMA fully substitutes for the discriminative stimulus effect of MDMA, indicative of similar subjective effects. Although there is currently no data that has directly assessed the psychological or physiological dependence liability of PMMA, its pharmacological similarities to MDMA suggest it likely has low physical dependence liability similar to that of MDMA. Evidence demonstrates that users of PMMA seem to be seeking MDMA, which may be mixed with PMMA. Because PMMA shares a pharmacological mechanism of action and psychoactive effects similar to the schedule 1 substance MDMA, PMMA has a high potential for abuse.

(2) The Drug or Substance Has No Currently Accepted Medical Use in Treatment in the United States

According to HHS, FDA has not approved any marketing application for a drug product containing PMMA for any indication. In addition, there are no clinical studies or petitioners that have claimed an accepted medical use of PMMA in the United States. Thus, PMMA has no currently accepted medical use in treatment in the United States.\10\

\10\ Although there is no evidence suggesting that PMMA has a currently accepted medical use in treatment in the United States, it bears noting that a drug cannot be found to have such medical use unless DEA concludes that it satisfies a five-part test. Specifically, with respect to a drug that has not been approved by FDA, to have a currently accepted medical use in treatment in the United States, all of the following must be demonstrated:

i. The drug's chemistry must be known and reproducible;

ii. there must be adequate safety studies;

iii. there must be adequate and well-controlled studies proving efficacy;

iv. the drug must be accepted by qualified experts; and

v. the scientific evidence must be widely available.

57 FR 10499 (1992).

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(3) There Is a Lack of Accepted Safety for Use of the Drug or Substance Under Medical Supervision

Because PMMA has no approved medical use in treatment in the United States and has not been investigated as a new drug, its safety for use under medical supervision has not been determined. Therefore, there is a lack of accepted safety for use of PMMA under medical supervision.

Based on these findings, the Acting Administrator of DEA concludes that PMMA warrants control in schedule I of the CSA. **21 U.S.C. 812(b)(1).** More precisely, because PMMA shares a pharmacological mechanism of action and psychoactive effects similar to the schedule 1 substance MDMA, DEA is proposing to place PMMA in **21 CFR 1308.11(d)** (the hallucinogenic category of schedule I). As such, the proposed control of PMMA includes the substance, as well as its salts, isomers, and salts of isomers whenever the existence of such isomers and salts is possible, within the specific chemical designation.

Requirements for Handling PMMA

If this rule is finalized as proposed, PMMA would be subject to the CSA's schedule I regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, reverse distribution, import, export, engagement in research, conduct of instructional activities or chemical analysis with, and possession of schedule I controlled substances, including the following:

1. *Registration.* Any person who handles (manufactures, distributes, reverse distributes, imports, exports, engages in research, or conducts instructional activities or chemical analysis with, or possesses) PMMA, or who desires to handle PMMA, would need to be registered with DEA to conduct such activities pursuant to **21 U.S.C. 822, 823, 957, 958,** and in accordance with **21 CFR parts 1301** and **1312,** as of the effective date of a final scheduling action. Any person who currently handles PMMA, and is not registered with DEA, would need to submit an application for registration and may not continue to handle PMMA after the effective date of a final scheduling action unless DEA has approved that application for registration pursuant to 21 U.S.C. 822, 823, 957, 958, and in accordance with 21 CFR parts 1301 and 1312.

2. *Disposal of stocks.* Any person who does not desire or is not able to obtain a schedule I registration would be required to surrender all quantities of currently held PMMA or transfer all quantities of currently held PMMA to a person registered with DEA before the effective date of a final scheduling action, in accordance with all applicable Federal, State, local, and tribal laws. As of the effective date of a final scheduling action, PMMA would be required to be disposed of in accordance with **21 CFR part 1317,** in addition to all other applicable Federal, State, local, and tribal laws.

3. *Security.* PMMA would be subject to schedule I security requirements and would need to be handled and stored in accordance with **21 CFR 1301.71-1301.93** as of the effective date of a final scheduling action.

4. *Labeling and Packaging.* All labels, labeling, and packaging for commercial containers of PMMA would need to be in compliance with **21 U.S.C. 825** and **958(e),** and be in accordance with **21 CFR part 1302,** as of the effective date of a final scheduling action.

5. *Quota.* Only registered manufacturers would be permitted to manufacture PMMA in accordance with a quota assigned, pursuant to **21 U.S.C. 826** and in accordance with **21 CFR part 1303,** as of the effective date of a final scheduling action.

6. *Inventory.* Every DEA registrant who possesses any quantity of PMMA on the effective date of a final scheduling action would be required to take an inventory of PMMA on hand at that time, pursuant to **21 U.S.C. 827** and **958,** and in accordance with **21 CFR 1304.03, 1304.04,** and **1304.11(a)** and (d).

Any person who becomes registered with DEA on or after the effective date of the final scheduling action would be required to take an initial inventory of all stocks of controlled substances (including PMMA) on hand on the date the registrant first engages in the handling of controlled substances, pursuant to **21 U.S.C. 827** and **958,** and in accordance with **21 CFR 1304.03, 1304.04,** and **1304.11(a)** and (b).

After the initial inventory, every DEA registrant would be required to take an inventory of all controlled substances (including PMMA) on hand every two years, pursuant to **21 U.S.C. 827** and **958,** and in accordance with **21 CFR 1304.03, 1304.04,** and **1304.11.**

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7. *Records and Reports.* Every DEA registrant would be required to maintain records and submit reports for PMMA, or products containing PMMA, pursuant to **21 U.S.C. 827** and **958,** and in accordance with **21 CFR parts 1304, 1312,** and **1317,** as of the effective date of a final scheduling action. Manufacturers and distributors would be required to submit reports regarding PMMA to the Automation of Reports and Consolidated Order System pursuant to 21 U.S.C. 827 and in accordance with 21 CFR parts 1304 and 1312, as of the effective date of a final scheduling action.

8. *Order Forms.* Every DEA registrant who distributes PMMA would be required to comply with order form requirements, pursuant to **21 U.S.C. 828,** and in accordance with **21 CFR part 1305,** as of the effective date of a final scheduling action.

9. *Importation and Exportation.* All importation and exportation of PMMA would need to be in compliance with **21 U.S.C. 952**, **953**, **957**, and **958**, and in accordance with **21 CFR part 1312**, as of the effective date of a final scheduling action.

10. *Liability.* Any activity involving PMMA not authorized by, or in violation of, the CSA or its implementing regulations, would be unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

Regulatory Analyses

Executive Orders 12866, 13563, and 13771, Regulatory Planning and Review, Improving Regulation and Regulatory Review, and Reducing Regulation and Controlling Regulatory Costs

In accordance with **21 U.S.C. 811**(a), this proposed scheduling action is subject to formal rulemaking procedures performed "on the record after opportunity for a hearing," which are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth the procedures and criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget (OMB) pursuant to section 3(d)(1) of Executive Order 12866 and the principles reaffirmed in Executive Order 13563.

This rulemaking is not an Executive Order 13771 regulatory action because this rule is not significant under Executive Order 12866.

Executive Order 12988, Civil Justice Reform

This proposed regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of Executive Order 12988, Civil Justice Reform, to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132, Federalism

This proposed rulemaking does not have federalism implications warranting the application of Executive Order 13132. The proposed rule does not have substantial direct effects on the States, on the relationship between the national government and the States, or the distribution of power and responsibilities among the various levels of government.

Executive Order 13175, Consultation and Coordination With Indian Tribal Governments

This proposed rule does not have tribal implications warranting the application of Executive Order 13175. It does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal Government and Indian tribes, or on the distribution of power and responsibilities between the Federal Government and Indian tribes.

Regulatory Flexibility Act

The Acting Administrator, in accordance with the Regulatory Flexibility Act, 5 U.S.C. 601-602, has reviewed this proposed rule, and by approving it, certifies that it will not have a significant economic impact on a substantial number of small entities.

DEA proposes placing the substance PMMA (chemical name: 1-(4-methoxyphenyl)-*N*-methylpropan-2-amine), including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible, in schedule I of the CSA. This action is being taken to enable the United States to meet its obligations under the 1971 Convention on Psychotropic Substances. If finalized, this action would impose the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances on persons who handle (manufacture, distribute, reverse distribute, import, export, engage in research, conduct instructional activities or chemical analysis with, or possess), or propose to handle PMMA.

According to HHS, PMMA has a high potential for abuse, has no currently accepted medical use in treatment in the United States, and lacks accepted safety for use under medical supervision. DEA's research confirms that there is no legitimate commercial market for PMMA in the United States. Therefore, DEA estimates that no United States entity currently handles PMMA and does not expect any United States entity to handle PMMA in the foreseeable future. DEA concludes that no legitimate United States entity would be affected by this rule if finalized. As such, the proposed rule will not have a significant effect on a substantial number of small entities.

Unfunded Mandates Reform Act of 1995

In accordance with Unfunded Mandates Reform Act (UMRA) of 1995, 2 U.S.C. 1501 et seq., DEA has determined and certifies that this action would not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million or more (adjusted annually for inflation) in any 1 year * * *." Therefore, neither a Small Government Agency Plan nor any other action is required under UMRA of 1995.

Paperwork Reduction Act of 1995

This action does not impose a new collection of information under the Paperwork Reduction Act of 1995. 44 U.S.C. 3501-3521. This action would not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, 21 CFR part 1308 is proposed to read as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

- 1. The authority citation for 21 CFR part 1308 continues to read as follows:

  Authority: **21 U.S.C. 811**, **812**, **871**(b), **956**(b), unless otherwise noted.

- 2. In **Sec. 1308.11**, add paragraph (d)(80) to read as follows:

Sec. 1308.11 Schedule I.

* * * * *

(d) * * *

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(79) 1-(4-methoxyphenyl)-*N*-methylpropan-2-amine (other names: *para*-methoxymethamphetamine, PMMA)	1245

* * * * *

Uttam Dhillon,
Acting Administrator.

[FR Doc. 2020-09599 Filed 5-14-20; 8:45 am]

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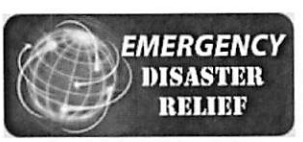

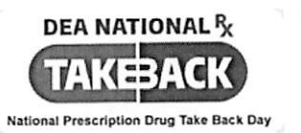

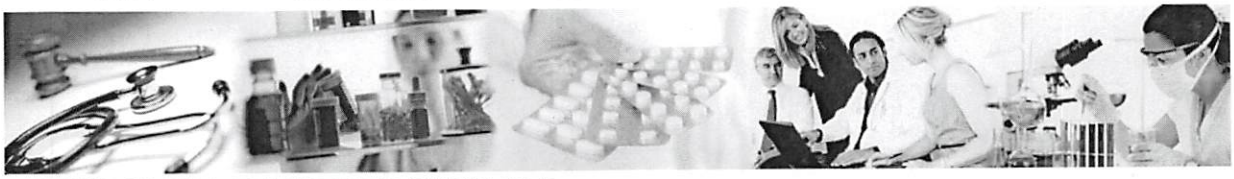

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PART 1308 — SCHEDULES OF CONTROLLED SUBSTANCES

EXCLUDED NONNARCOTIC SUBSTANCES

SCHEDULES

§1308.12 Schedule II.

(a) Schedule II shall consist of the drugs and other substances, by whatever official name, common or usual name, chemical name, or brand name designated, listed in this section. Each drug or substance has been assigned the Controlled Substances Code Number set forth opposite it.

(b) *Substances, vegetable origin or chemical synthesis.* Unless specifically excepted or unless listed in another schedule, any of the following substances whether produced directly or indirectly by extraction from substances of vegetable origin, or independently by means of chemical synthesis, or by a combination of extraction and chemical synthesis:

(1) Opium and opiate, and any salt, compound, derivative, or preparation of opium or opiate excluding apomorphine, thebaine-derived butorphanol, dextrorphan, nalbuphine, naldemedine, nalmefene, naloxegol, naloxone, 6β-naltrexol and naltrexone, and their respective salts, but including the following:

(i) Codeine	9050
(ii) Dihydroetorphine	9334
(iii) Ethylmorphine	9190
(iv) Etorphine hydrochloride	9059
(v) Granulated opium	9640
(vi) Hydrocodone	9193
(vii) Hydromorphone	9150
(viii) Metopon	9260
(ix) Morphine	9300
(x) Noroxymorphone	9668
(xi) Opium extracts	9610
(xii) Opium fluid	9620
(xiii) Oripavine	9330
(xiv) Oxycodone	9143
(xv) Oxymorphone	9652
(xvi) Powdered opium	9639
(xvii) Raw opium	9600
(xviii) Thebaine	9333
(xix) Tincture of opium	9630

(2) Any salt, compound, derivative, or preparation thereof which is chemically equivalent or identical with any of the substances referred to in paragraph (b) (1) of this section, except that these substances shall not include the isoquinoline alkaloids of opium.

(3) Opium poppy and poppy straw.

(4) Coca leaves (9040) and any salt, compound, derivative or preparation of coca leaves (including cocaine (9041) and ecgonine (9180) and their salts, isomers, derivatives and salts of isomers and derivatives), and any salt, compound, derivative, or preparation thereof which is chemically equivalent or identical with any of these substances, except that the substances shall not include:

(i) Decocainized coca leaves or extraction of coca leaves, which extractions do not contain cocaine or ecgonine; or

(ii) [^{123}I]ioflupane.

(5) Concentrate of poppy straw (the crude extract of poppy straw in either liquid, solid or powder form which contains the phenanthrene alkaloids of the opium poppy), 9670.

(c) *Opiates.* Unless specifically excepted or unless in another schedule any of the following opiates, including its isomers, esters, ethers, salts and salts of isomers, esters and ethers whenever the existence of such isomers, esters, ethers, and salts is possible within the specific chemical designation, dextrorphan and levopropoxyphene excepted:

(1) Alfentanil	9737
(2) Alphaprodine	9010
(3) Anileridine	9020
(4) Bezitramide	9800
(5) Bulk dextropropoxyphene (non-dosage forms)	9273
(6) Carfentanil	9743
(7) Dihydrocodeine	9120
(8) Diphenoxylate	9170
(9) Fentanyl	9801
(10) Isomethadone	9226
(11) Levo-alphacetylmethadol [Some other names: levo-alpha-acetylmethadol, levomethadyl acetate, LAAM]	9648
(12) Levomethorphan	9210
(13) Levorphanol	9220

(14) Metazocine	9240
(15) Methadone	9250
(16) Methadone-Intermediate, 4-cyano-2-dimethylamino-4,4-diphenyl butane	9254
(17) Moramide-Intermediate, 2-methyl-3-morpholino-1, 1-diphenylpropane-carboxylic acid	9802
(18) Oliceridine (*N*-[(3-methoxythiophen-2-yl)methyl] ({2-[(9*R*)-9-(pyridin-2-yl)-6-oxaspiro [4.5]decan-9-yl]ethyl})amine fumarate)	9245
(19) Pethidine (meperidine)	9230
(20) Pethidine-Intermediate-A, 4-cyano-1-methyl-4-phenylpiperidine	9232
(21) Pethidine-Intermediate-B, ethyl-4-phenylpiperidine-4-carboxylate	9233
(22) Pethidine-Intermediate-C, 1-methyl-4-phenylpiperidine-4-carboxylic acid	9234
(23) Phenazocine	9715
(24) Piminodine	9730
(25) Racemethorphan	9732
(26) Racemorphan	9733
(27) Remifentanil	9739
(28) Sufentanil	9740
(29) Tapentadol	9780
(30) Thiafentanil	9729

(d) *Stimulants.* Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of the following substances having a stimulant effect on the central nervous system:

(1) Amphetamine, its salts, optical isomers, and salts of its optical isomers	1100
(2) Methamphetamine, its salts, isomers, and salts of its isomers	1105
(3) Phenmetrazine and its salts	1631
(4) Methylphenidate	1724
(5) Lisdexamfetamine, its salts, isomers, and salts of its isomers	1205

(e) *Depressants.* Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of the following substances having a depressant effect on the central nervous system, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation:

(1) Amobarbital	2125
(2) Glutethimide	2550
(3) Pentobarbital	2270
(4) Phencyclidine	7471
(5) Secobarbital	2315

(f) *Hallucinogenic substances.*

(1) Nabilone	7379
[Another name for nabilone: (+/-)-*trans*-3-(1,1-dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6, 6-dimethyl-9H-dibenzo[b,d]pyran-9-one]	
(2) Dronabinol [(-)-delta-9-*trans* tetrahydrocannabinol] in an oral solution in a drug product approved for marketing by the U.S. Food and Drug Administration	7365

(g) *Immediate precursors.* Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of the following substances:

(1) Immediate precursor to amphetamine and methamphetamine:

(i) Phenylacetone	8501
Some trade or other names: phenyl-2-propanone; P2P; benzyl methyl ketone; methyl benzyl ketone;	

(2) Immediate precursors to phencyclidine (PCP):

(i) 1-phenylcyclohexylamine	7460
(ii) 1-piperidinocyclohexanecarbonitrile (PCC)	8603

(3) Immediate precursor to fentanyl:

(i) 4-anilino-N-phenethylpiperidine (ANPP)	8333
(ii) *N*-phenyl-*N*-(piperidin-4-yl)propionamide (norfentanyl)	8366

[39 FR 22142, June 20, 1974]

Editorial Note: For Federal Register citations affecting §1308.12, see the List of CFR Sections Affected, which appears in the Finding Aids section of the printed volume and at www.govinfo.gov.

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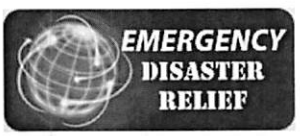

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DIVERSION CONTROL DIVISION

Rules - 2020

[Federal Register Volume 85, Number 238 (Thursday, December 10, 2020)]
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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-665]

Schedules of Controlled Substances: Removal of Samidorphan From Control

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Drug Enforcement Administration (DEA) proposes to remove samidorphan (3-carboxamido-4-hydroxy naltrexone) and its salts from the schedules of the Controlled Substances Act (CSA). This scheduling action is pursuant to the CSA which requires that such actions be made on the record after opportunity for a hearing through formal rulemaking. Samidorphan is currently a schedule II controlled substance because it can be derived from opium alkaloids. This action would remove the regulatory controls and administrative, civil, and criminal sanctions applicable to controlled substances, including those specific to schedule II controlled substances, on persons who handle (manufacture, distribute, reverse distribute, dispense, conduct research, import, export, or conduct chemical analysis) or propose to handle samidorphan.

DATES: Interested persons may file written comments on this proposal in accordance with **21 CFR 1308.43**(g). Electronic comments must be submitted, and written comments must be postmarked, on or before January 11, 2021. Commenters should be aware that the electronic Federal Docket Management System will not accept comments after 11:59 p.m. Eastern Time on the last day of the comment period.

Interested persons may file a request for hearing or waiver of participation pursuant to **21 CFR 1308.44** and in accordance with **21 CFR 1316.45**, **1316.47**, **1316.48**, or **1316.49**, as applicable. Requests for hearing, notices of appearance, and waivers of an opportunity for a hearing or to participate in a hearing must be received on or before January 11, 2021.

ADDRESSES: To ensure proper handling of comments, please reference "Docket No. DEA-665" on all correspondence, including any attachments.

- *Electronic comments:* DEA encourages that all comments be submitted through the Federal eRulemaking Portal, which provides the ability to type short comments directly into the comment field on the web page or to attach a file for lengthier comments. Please go to http://www.regulations.gov and follow the online instructions at that site for submitting comments. Upon completion of your submission you will receive a Comment Tracking Number for your comment. Please be aware that submitted comments are not instantaneously available for public view on Regulations.gov. If you have received a comment tracking number, your comment has been successfully submitted and there is no need to resubmit the same comment.
- *Paper comments:* Paper comments that duplicate an electronic submission are not necessary and are discouraged. Should you wish to mail a comment in lieu of an electronic format, it should be sent via regular or express mail to: Drug Enforcement Administration, Attention: DEA Federal Register Representative/DPW, 8701 Morrissette Drive, Springfield, Virginia 22152.
- *Hearing requests:* All requests for hearing and waivers of participation must be sent to: Drug Enforcement Administration, Attn: Hearing Clerk/OALJ, 8701 Morrissette Drive, Springfield, Virginia 22152.

FOR FURTHER INFORMATION CONTACT: Terrence L. Boos, Drug & Chemical Evaluation Section, Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (571) 362-3261.

SUPPLEMENTARY INFORMATION:

Posting of Public Comments

Please note that all comments received in response to this docket are considered part of the public record. They will, unless reasonable cause is given, be made available by DEA for public inspection online at http://www.regulations.gov. Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter. The Freedom of Information Act applies to all comments received. If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want it to be made publicly available, you must include the phrase "PERSONAL IDENTIFYING INFORMATION" in the first paragraph

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of your comment. You must also place the personal identifying information you do not want made publicly available in the first paragraph of your comment and identify what information you want redacted.

If you want to submit confidential business information as part of your comment, but do not want it to be made publicly available, you must include the phrase "CONFIDENTIAL BUSINESS INFORMATION" in the first paragraph of your comment. You must also prominently identify confidential business information to be redacted within the comment.

Comments containing personal identifying information and confidential business information identified as directed above will generally be made publicly available in redacted form. If a comment has so much confidential business information or personal identifying information that it cannot be effectively redacted, all or part of that comment may not be made publicly available. Comments posted to http://www.regulations.gov may include any personal identifying information (such as name, address, and phone number) included in the text of your electronic submission that is not identified as directed above as confidential.

An electronic copy of this document and supplemental information to this proposed rule are available at http://www.regulations.gov for easy reference. DEA specifically solicits written comments regarding DEA's economic analysis of the impact of these proposed changes. DEA requests that commenters provide detailed descriptions in their comments of any expected economic impacts, especially to small entities. Commenters should provide empirical data to illustrate the nature and scope of such impact.

Request for Hearing, Notice of Appearance at or Waiver of Participation in Hearing

Pursuant to 21 U.S.C. 811(a), this action is a formal rulemaking "on the record after opportunity for a hearing." Such proceedings are conducted pursuant to the provisions of the Administrative Procedure Act (5 U.S.C. 551-559). 21 CFR 1308.41-1308.45, and 21 CFR part 1316 subpart D. In accordance with 21 CFR 1308.44 (a)-(c), requests for hearing, notices of appearance, and waivers of an opportunity for a hearing or to participate in a hearing may be submitted by interested persons. Such requests or notices must conform to the requirements of 21 CFR 1308.44(a) or (b), and 1316.47 or 1316.48, as applicable, and include a statement of the interest of the person in the proceeding and the objections or issues, if any, concerning which the person desires to be heard. Any waiver must conform to the requirements of 21 CFR 1308.44(c) and 1316.49, including a written statement regarding the interested person's position on the matters of fact and law involved in any hearing.

Please note that, pursuant to 21 U.S.C. 811(a)(2), the purpose of a hearing would be to determine whether samidorphan should be removed from the list of controlled substances based on a finding that the drug does not meet the requirements for inclusion in any schedule. All requests for hearing and waivers of participation must be sent to DEA using the address information above, on or before the date specified above.

Legal Authority

The CSA provides that proceedings for the issuance, amendment, or repeal of the scheduling of any drug or other substance may be initiated by the Attorney General (1) on his own motion, (2) at the request of the Secretary of the Department of Health and Human Services (HHS),\1\ or (3) on the petition of any interested party. 21 U.S.C. 811(a). This action was initiated by a petition to remove samidorphan from the list of scheduled controlled substances of the CSA, and is supported by, inter alia, a recommendation from the Assistant Secretary of HHS and an evaluation of all relevant data by DEA. If finalized, this action would remove the regulatory controls and administrative, civil, and criminal sanctions applicable to controlled substances, including those specific to schedule II controlled substances, on persons who handle or propose to handle samidorphan.

\1\ As discussed in a memorandum of understanding entered into by the Food and Drug Administration (FDA) and NIDA, FDA acts as the lead agency within the HHS in carrying out the Secretary's scheduling responsibilities under the CSA, with the concurrence of NIDA. 50 FR 9518, March 8, 1985. The Secretary of the HHS has delegated to the Assistant Secretary for Health of the HHS the authority to make domestic drug scheduling recommendations. 58 FR 35460, July 1, 1993.

Background

Samidorphan (3-carboxamido-4-hydroxy naltrexone), is a chemical entity that is structurally similar to naltrexone, a mu (μ)-opioid receptor antagonist. Samidorphan (other developmental code names: RDC-0313 or ALKS 33) is a mu-opioid receptor antagonist with a weak partial agonist activity at the kappa (κ)- and delta (δ)-opioid receptors. According to HHS, products containing samidorphan are currently being developed for medical use.

Samidorphan is currently controlled in Schedule II of the CSA, as defined in 21 CFR 1308.12(b)(l), because it can be derived from opium alkaloids. On April 14, 2014, DEA received a petition to initiate proceedings to amend 21 CFR 1308.12(b)(1) so as to decontrol samidorphan from schedule II of the CSA. The petition complied with the requirements of 21 CFR 1308.43(b) and was accepted for filing. The petitioner contended that samidorphan has been characterized as an opioid receptor antagonist, a class of drugs with no abuse potential.

Proposed Determination To Decontrol Samidorphan

Pursuant to 21 U.S.C. 811(b), on April 24, 2015, DEA, having gathered the necessary data on samidorphan, forwarded that data and the petition to HHS \2\ with a request for scientific and medical evaluation and scheduling recommendation for samidorphan. On January 9, 2020, DEA received from HHS a scientific and medical evaluation (dated December 19, 2019) conducted by the Food and Drug Administration (FDA) entitled "Basis for the Recommendation to Remove Samidorphan (3-Carboxamido-4-Hydroxy Naltrexone) and its Salts from All Schedules of Control Under the Controlled Substances Act" and a scheduling recommendation. The National Institute on Drug Abuse (NIDA) concurred with the scientific and medical evaluation conducted by FDA. Based on the totality of the available scientific data, samidorphan does not conform with the findings for schedule II in 21 U.S.C. 812(b)(2) or in any other schedule as set forth in 21 U.S.C. 812(b). Based on FDA's scientific and medical review of the eight factors and findings related to the substance's abuse potential, legitimate medical use, and dependence liability, HHS recommended that samidorphan and its salts be removed from all schedules of control of the CSA.

\2\ Administrative responsibilities for evaluating a substance for control under the CSA are performed for HHS by the Food and Drug Administration (FDA), with the concurrence of NIDA, according to a Memorandum of Understanding (50 FR 9518; March 8, 1985).

The CSA requires DEA, as delegated by the Attorney General,\3\ to determine whether HHS's scientific and medical evaluation, scheduling recommendation, and all other relevant data constitute substantial evidence that a substance should be scheduled.

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21 U.S.C. 811(b). DEA reviewed the scientific and medical evaluation and scheduling recommendation provided by HHS, and all other relevant data, and completed its own eight-factor review document on samidorphan pursuant to 21 U.S.C. 811(c). Included below is a brief summary of each factor as analyzed by HHS and DEA, and as considered by DEA in this proposal to remove samidorphan from the schedules of the CSA. Please note that both DEA and HHS analyses are available in their entirety under "Supporting and Related Material" of the public docket for this rule at http://www.regulations.gov under docket number DEA-665.

\3\ 28 CFR 0.100(b).

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1. The Drug's Actual or Relative Potential for Abuse.

The first factor that must be considered is the actual or relative potential for abuse of samidorphan. The term "abuse" is not defined in the CSA. However, the legislative history of the CSA suggests the following points in determining whether a particular drug or substance has a potential for abuse: \4\

\4\ Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970); 1970 U.S.C.C.A.N. 4566, 4603.

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a. Whether there is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.

As stated by HHS, samidorphan is not readily available or marketed in any country, so there is a lack of evidence to date regarding samidorphan diversion, illicit manufacturing, or use outside of clinical trials. There are no anecdotal reports of samidorphan abuse in the published literature or in drug abuse discussion platforms (e.g., PubMed, erowid.org).

b. Whether there is significant diversion of the drug or drugs containing such a substance from legitimate drug channels.

According to HHS, there were no reports of diversion of samidorphan in clinical trials conducted with this substance. DEA further notes that there are no reports of law enforcement encounters of samidorphan in the National Forensic Laboratory Information System (NFLIS),\5\ the System to Retrieve Information from Drug Evidence (STRIDE) \6\ and STARLIMS \7\ (Queried October 14, 2020). Thus, there is no evidence of diversion of samidorphan.

\5\ The NFLIS is a national forensic laboratory reporting system that systematically collects results from drug chemistry analyses conducted by State and local forensic laboratories in the United States.

\6\ STRIDE is a database of drug exhibits sent to DEA laboratories for analysis. Exhibits from the database are from DEA, other federal agencies, and some local law enforcement agencies.

\7\ STARLIMS is a laboratory information management system that systematically collects results from drug chemistry analyses conducted by DEA laboratories. On October 1, 2014, STARLIMS replaced STRIDE as the DEA laboratory drug evidence data system of record.

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c. Whether individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice.

According to HHS, there is no evidence of individuals taking samidorphan on their own initiative. DEA notes that a review of scientific literature, STRIDE, STARLIMS, and NFLIS databases revealed no history of abuse of samidorphan. Thus, there is no evidence that individuals are taking samidorphan on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer the same. There are no anecdotal reports of samidorphan abuse in the published literature or in drug discussion platforms (e.g., PubMed, erowid.org, bluelight.org).

d. Whether the drug or drugs containing such a substance are new drugs so related in their action to a substance already listed as having a potential for abuse to make it likely that it will have the same potentiality for abuse as such drugs, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that they have a substantial capability of creating hazards to the health of the user or to the safety of the community.

According to HHS, actions of samidorphan are not related to a substance already listed as having a potential for abuse. There is no evidence that individuals are taking samidorphan to create a hazard to their health or to the safety of other individuals or to the community. Samidorphan is not currently marketed and there is no evidence of diversion of samidorphan from legitimate drug channels. There is no evidence that individuals are taking samidorphan on their own initiative without medical advice. Samidorphan is not related in its action to any known substance with abuse liability. Substances such as naloxone and naltrexone, with pharmacological effects of mu-opioid receptor antagonists similar to that of samidorphan, have been decontrolled under the CSA. Thus, these data collectively indicate that samidorphan has no potential for abuse.

2. Scientific Evidence of the Drug's Pharmacological Effects, If Known.

Preclinical studies

In Vitro Studies

According to HHS, opioid receptor binding and functional studies with samidorphan have been conducted in vitro in cloned human opioid receptors expressed in Chinese hamster ovary (CHO) cells. These studies showed that samidorphan binds to human mu- and kappa-opioid receptors with sub-nanomolar Ki values of 0.052 nM and 0.23 nM, respectively. Samidorphan also binds to the delta-opioid receptors with nanomolar affinity (Ki of 2.7 nM). These values demonstrate that, like the opioid receptor antagonist naltrexone, samidorphan has a high affinity for the mu- and kappa-opioid receptors. A cellular functional study with [35S]GTPγS assay in CHO cells further showed that samidorphan has subnanomolar antagonist activity at the mu-opioid receptor and is comparable to that of naltrexone.

Safety Pharmacology Studies

According to the HHS' review, several safety studies were conducted to determine the cardiovascular, respiratory, and neurological effects of the drug and can help determine if samidorphan has depressant, stimulant, or other psychoactive effects related to abuse potential.

Cardiovascular and Respiratory Effects

According to HHS, a study evaluating in vitro effects of samidorphan (0.5, 5, and 50 μM) on the QT-interval, QRS duration, contractility and maximum rate of contraction was conducted in isolated retrograde perfused rabbit heart preparation. Results showed that, at the lowest concentration, 0.5 μM, samidorphan significantly decreased contractility. But, samidorphan at 5 and 50 μM concentrations did not significantly affect contractility.

An animal study revealed the cardiovascular and pulmonary effects of orally administered (per os or PO) samidorphan (0.5, 3, and 10 mg/kg doses) in beagle dogs. The high doses of samidorphan resulted in several cases of emesis and excessive salivation. For pharmacokinetic (PK) measurements, animals were given either a low dose of 0.5 mg/kg or a high dose of 20 mg/kg of samidorphan. Male dogs given a single PO dose of samidorphan had average PK measurements of Cmax = 4320 ng/mL, T max = 1.2 hr, half-life = 4.1 hr, and AUC last = 30,500 hrng/mL. In regard to cardiac activity, the female and male groups produced a slight decrease in

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systolic blood pressure (an average insignificant decrease of 17 to 26 mm Hg) and no significant differences in cardiac contractility or body temperature. Based on the results, this investigation reported no observed adverse effects at the level of 10 mg/kg in beagle dogs. In the same study, samidorphan at any of the doses tested did not cause any significant effects on respiratory rate, tidal volume, and minute volume.

According to HHS' review, samidorphan reversed cardiac and respiratory effects produced by continuous intravenous infusion (IV) of fentanyl, a mu-opioid receptor agonist, in beagle dogs and Cynomolgus monkeys. Overall, samidorphan does not appear to produce mu-opioid receptor agonist related cardiac or pulmonary effects.

Central Nervous System Effects

According to HHS, central nervous system effects of samidorphan (3.5, 35, or 350 mg/kg, PO) on functional observational battery in a study conducted in Sprague-Dawley rats are most consistent with that of depressants such as opioids, cannabinoids, and GABAA channel modulators.

Unlike mu-opioid receptor agonists that typically produce analgesic effects in assays on thermal and inflammatory painful stimulation, samidorphan produced no measurable analgesic effects. In the hot plate test in male Sprague-Dawley rats, samidorphan did not produce thermal analgesia when administered subcutaneously (SC) at doses of 0.003 to 0.1 mg/kg or when administered intraperitoneally at doses in the range of 0.01 to 30 mg/kg. However, samidorphan blocked morphine-induced (15 mg/kg, SC) analgesia in rats with ED50 values of 0.01 mg/kg (SC administration) and 0.3 mg/kg (PO administration), respectively. Its blockade of morphine's analgesic effects lasted for approximately 4 hours. Because morphine is known to produce its analgesic effects as an agonist of the mu-opioid receptor, this study suggests that samidorphan blocks this mechanism of action similar to other mu-opioid receptor antagonists, such as naloxone and naltrexone, which also possess this blockade effect.

In a tail-flick assay used to measure thermal-nociception, the result showed that administered subcutaneously samidorphan did not produce analgesia up to the highest dose tested of 10 mg/kg. Furthermore, samidorphan antagonized morphineinduced anti-nociception when administered either SC or PO. These data indicate that samidorphan acts as an antagonist at the mu-opioid receptor because it blocked the analgesic effects of the mu-opioid receptor agonist morphine without producing analgesic effects of its own.

Abuse Liability Studies

Effects on Ethanol Self-Administration

According to HHS, a self-administration study in male Wistar rats was conducted to determine if samidorphan has effects similar to that of other opioid receptor antagonists such as naltrexone in reducing ethanol drinking behavior. Rats were trained to self-administer ethanol on a fixed ratio (FR) 2 schedule of reinforcement. Effects of samidorphan (0 to 3 mg/kg, SC) administered 30 minutes prior to the placement of the rats into the test cages on ethanol drinking behavior were studied. Naltrexone, the positive control drug (3 or 6 mg/kg, SC), was only able to decrease lever responding by approximately 75 percent. The highest dose of samidorphan (3 mg/kg, SC) decreased lever responding by approximately 50 percent. According to HHS, these data demonstrate that pretreatment with samidorphan can decrease, but not eliminate, the reinforcing effects of 10 percent ethanol and these results are consistent with that of other mu-opioid receptor antagonists such as naltrexone, which is indicated for the treatment of alcohol dependence.

Drug Discrimination Studies

Drug discrimination assays in animals can be used to predict if a test drug will have abuse potential in humans. According to HHS, a drug discrimination study was conducted to test the stimulus effects of samidorphan in rats trained to discriminate the stimulus effects of subcutaneously administered morphine (3 mg/kg) to its vehicle (0.9 percent sodium chloride for injection, USP) in a two-lever operant chamber on a FR10 schedule of reinforcement. Samidorphan (0.1, 0.3, 1 or 3 mg/kg) did not generalize to the morphine cue. Samidorphan did not affect lever press response rates indicating that the rats were not incapacitated by the drug. These data indicate that samidorphan does not produce a discriminative cue similar to that of morphine (at 3 mg/kg).

Self-Administration Studies

HHS cited two self-administration studies assessing the reinforcing effects of samidorphan in rats. In the first study, rats were trained to lever press on a FR5 schedule for intravenous self-administration of morphine (0.56 mg/kg/injection). When samidorphan was tested at 0.0136, 0.0408, and 0.068 mg/kg/injection, the animals did not respond at levels seen with the positive control, morphine. Therefore, it was concluded that samidorphan did not produce reinforcing effects similar to that of morphine in rats. However, the total number of infusions of samidorphan was statistically higher than the vehicle. According to HHS, this could have been the result of the inadequate extinction due to the reintroduction of the training drug between doses of samidorphan; this could have artificially inflated the responding of samidorphan because animals never fully underwent extinction. As a result, a second self-administration study with heroin as the training drug using FR5 and a progressive schedule of reinforcement was conducted. There was no reintroduction of the training drug between doses of samidorphan with an additional referred arm of naltrexone. The result showed that the number of samidorphan (0.068 mg/kg/injection) injections, similar to naltrexone, was significantly higher than the number of saline injections, but was significantly lower than that of heroin. A progressive ratio schedule of reinforcement is used to determine the reinforcing efficacy of a drug by measuring the break point. A breakpoint is defined as the number of operant responses (lever presses) at which the subject ceases self-administration of the reinforcer. Results of the study using the PR schedule of reinforcement were similar to that of the FR5 study: All doses of samidorphan tested produced breakpoints that were significantly lower than heroin and only the highest dose of samidorphan (0.068 mg/kg/injection) was significantly higher than saline. Importantly, naltrexone, tested at the same doses as samidorphan, produced results similar to that of samidorphan. According to HHS, these studies suggest that samidorphan has a profile similar to that of naltrexone and does not produce statistically significant reinforcing effects.

Intra-Cranial Self-Stimulation Study

Intracranial self-stimulation (ICSS) is a behavioral study that can be used to evaluate brain rewarding or aversive effects of drugs. HHS provided an ICSS study report of samidorphan in rats. Following implantation with permanent indwelling electrodes in the right medial forebrain at the level of the lateral hypothalamus, the animals were trained to respond (i.e., lever press) to

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receive brain stimulation.\8\ Baseline ICSS training generated a frequency response curve where increasing the intensity of brain stimulation increased the rate of lever pressing. After baseline ICSS levels were established, rats were administered several doses of samidorphan. The subcutaneous administration of samidorphan at doses of 0.03, 0.1, 0.3, and 1.0 mg/kg did not shift the frequency response curve relative to baseline and did not change the maximum rate of responding. This study indicates that samidorphan does not affect the brain reward pathway in rats.

\8\ This statement and the subsequent content in this paragraph are based on the revised information provided under MOU by FDA/Controlled Substance Staff (CSS).

Clinical Abuse Liability Studies

The HHS review describes two studies to assess the abuse potential of samidorphan in human subjects. The first one, a randomized, double-blind, placebo and positive control, crossover study was to compare samidorphan (2.5, 10, and 20 mg, PO), oxycodone (15 and 30 mg, PO), and the placebo in 41 non-dependent recreational opioid users. The primary pharmacodynamic (PD) assessment was At the Moment Drug Liking measured by a visual analog scale (VAS), with secondary endpoints that measured Overall Drug Liking, Take Drug Again, and Alertness, all on a bipolar VAS. High, Good Effects and Bad Effects were measured on a unipolar VAS. Oxycodone at 30 and 15 mg doses produced mean Drug Liking scores of 81 and 73.3, respectively and these scores were significantly higher than the placebo. All three doses of samidorphan produced At the Moment Drug Liking, Overall Drug Liking, and Take Drug Again scores that were not significantly different from the placebo (50 to 51). There was one report (2.1 percent) of euphoria as an adverse event (AE) after taking samidorphan (20 mg) versus 11 reports (22.4 percent) following the positive control oxycodone dose (30 mg). This study concluded that samidorphan does not produce PD measurements that are consistent with abuse potential.

A second abuse potential study was conducted by using a placebo (PO), samidorphan (10 and 30 mg, PO), oxycodone (40 mg, PO), pentazocine (30 mg, IV), and naltrexone (100 mg, IV) in 42 healthy non-dependent recreational opioid users. The primary PD assessment was At the Moment Drug Liking measured by the bipolar VAS, with secondary endpoints that measured Overall Drug Liking, Take Drug Again, and Alertness. The study also took PK measurements to determine a correlation between blood levels and time of onset of the PD assessment. The positive controls, oxycodone (40 mg) and pentazocine (30 mg), produced the Emax of Drug Liking VAS scores of 76.1 and 82, respectively and these were significantly higher than the placebo. The Emax drug liking scores following 10 and 30 mg samidorphan were not significantly different from the placebo or naltrexone (100 mg). Euphoric mood was indicated as an AE in 30 subjects (53.6 percent) for oxycodone and in 30 subjects (52.6 percent) for pentazocine. The 30 and 10 mg doses of samidorphan produced a euphoric mood as an AE in 9 (15 percent) and 7 (12.3 percent) subjects, respectively; however, 5 subjects (8.6 percent) reported euphoria when receiving naltrexone, and 5 subjects (8.8 percent) reported euphoria when receiving the placebo. There were no reports of abuse of the drug or diversion in the study. HHS concludes that samidorphan produces stimulus effects similar to the placebo and naltrexone and does not have abuse potential. DEA notes that a recent peer-reviewed published clinical report describes that samidorphan, similar to a placebo and naltrexone, lacks abuse potential.

In summary, data from in vitro studies showed that samidorphan is a mu-opioid receptor antagonist with weak partial agonist activity at the kappa- and delta-opioid receptors. Data from in vivo studies further supported this conclusion; samidorphan blocked the analgesic effects of the mu-opioid receptor agonist morphine and the respiratory depressive effects of fentanyl. Samidorphan neither produced a discriminative cue similar to that of morphine nor had reinforcing effects in in vivo abuse liability studies in animals. Data from two clinical abuse potential studies suggested that samidorphan does not produce drug liking scores similar to oxycodone (a mu-opioid receptor agonist) or pentazocine (a kappa-opioid receptor agonist); instead, drug liking scores produced by samidorphan were similar to the negative controls, placebo and naltrexone. Overall, these data support the conclusion that samidorphan does not have abuse liability.

3. The State of Current Scientific Knowledge Regarding the Drug or Other Substance.

Samidorphan's molecular formula is C21H26N2O4 with a molecular weight of 370.44 g/mol. Currently, there are two salt forms, a hydrochloric acid salt (RDC-0313-01; molecular weight is 406.90 g/mol) and a malic acid salt (RDC-0313-02; molecular weight is 504.53 g/mol). Samidorphan is a derivative of naltrexone and it shares structural similarity with naltrexone. A multi-step process of samidorphan synthesis starts with naltrexone, with an end product of its malate salt.

According to HHS, samidorphan is rapidly absorbed both orally and sublingually. The Tmax is approximately 60 minutes after orally dosing, with a half-life of six to eight hours depending on the dose. The plasma levels of samidorphan increase linearly with each dose and it rapidly distributes throughout the body. Samidorphan is metabolized into two main products, RDC-9986 (N-dealkylated metabolite) and RDC-1066 (N-oxide metabolite), and they can be detected in human plasma at greater than 10 percent of the total drug-related exposure. Both RDC-9986 and RDC-1066 have nanomolar affinity for the mu-, kappa-, and delta-opioid receptors. RDC-9986 is an agonist at all three opioid receptors whereas RDC-1066 showed antagonist activity at the mu-opioid receptor as assessed by the [\35\S]GTPγS functional assay. DEA further notes that samidorphan has been reported to have high bioavailability following both sublingual and oral administration, it is not subject to extensive first-pass metabolism, and the PK parameters are not affected by food or age in health volunteers.

In summary, samidorphan shares chemical structural features with mu-opioid antagonists such as naltrexone. It is synthesized from the non-controlled substance naltrexone. Samidorphan exhibits high oral bioavailability and is rapidly absorbed. Clinical studies suggest that samidorphan was generally well-tolerated following single and multiple doses. RDC-9986 and RDC-1066, the two main metabolites of samidorphan, though they bind to opioid receptors, do not contribute significantly to pharmacodynamics of samidorphan.

4. Its History and Current Pattern of Abuse.

According to HHS, samidorphan has not been marketed in any country and thus information about the history and current pattern of its abuse is not available. Preclinical and clinical studies evaluating abuse potential of samidorphan did not show any abuse-related signals (see Factor 1 and 2, DEA and HHS Eight Factor Analyses). Instead, samidorphan showed effects similar to those of mu-opioid antagonists, a class of drugs not known to have abuse potential. The opioid antagonists, naloxone and naltrexone, were both originally schedule II

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substances as "opiate derivatives," and both are synthesized from thebaine. However, because they lacked opioid agonist activity, these were decontrolled in 1974 (naloxone), and in 1975 (naltrexone). More recently, the opioid antagonist naloxegol, a FDA-approved drug for the treatment of opioid induced constipation, was decontrolled in 2015. In addition, as mentioned earlier (see Factor 1, DEA and HHS Eight Factor Analyses), NFLIS, STRIDE, and STARLIMS had no mentions of samidorphan.

5. The Scope, Duration, and Significance of Abuse.

As stated by HHS, information about the scope, duration, and significance of samidorphan abuse is not available because it has not been marketed in any country. As mentioned in Factor 4 (DEA and HHS Eight Factor Analyses), a comprehensive review and research on available databases performed by both HHS and DEA revealed no reports of abuse of samidorphan. Data from preclinical and clinical studies showed no evidence of abuse potential for samidorphan. As stated by HHS, samidorphan upon its approval and availability for marketing is unlikely to be abused.

6. What, if any, Risk There is to the Public Health.

Based on the data and scientific information of preclinical and clinical study data reviewed by both HHS and DEA, there are no signals that indicate that samidorphan has abuse potential (see Factor 1 and 2, DEA and HHS Eight Factor Analyses). Currently, there is no evidence of drug dependence, abuse, and diversion. Thus, there is likely to be little or no risk of abuse and public health risk from samidorphan if it becomes available on the market.

7. Its Psychic or Physiological Dependence Liability.

According to HHS, several long-term toxicology studies were conducted using samidorphan in rats and dogs lasting 13, 26, or 39 weeks at doses of 250, 50, and 10 mg/kg/day. The animals were continually monitored after the study for withdrawal signs, such as weight changes, food consumption, morbidity, mortality, and locomotion effects. These studies did not find any behaviors or physical manifestations that were different from the control groups, indicating that samidorphan lacks potential to produce physical dependence. Data from these clinical studies showed no signals related to withdrawal or physical dependence.

The lack of samidorphan's ability to function as a positive reinforcer in self-administration studies in animals suggests that the use of samidorphan will not lead to psychological dependence. Similar to naltrexone (see Factor 2, DEA and HHS Eight Factor Analyses), samidorphan would not be expected to produce psychological dependence, and no evidence of psychological dependence was observed in clinical studies.

8. Whether the Substance is an Immediate Precursor of a Substance Already Controlled Under the CSA.

Samidorphan is not considered an immediate precursor of any controlled substance listed under the CSA as defined by **21 U.S.C. 802**(23).

Conclusion

Based on consideration of the scientific and medical evaluation and accompanying recommendation of HHS, and based on DEA's consideration of its own eight-factor analysis, DEA finds that these facts and all relevant data demonstrate that samidorphan does not possess abuse or dependence potential. According to HHS, medical product formulations containing samidorphan are under development. However, the finding that samidorphan lacks abuse potential would, irrespective of other findings, permit decontrol of samidorphan prior to or in the absence of an FDA action under 21 U.S.C. 355(c). Therapeutic and supratherapeutic doses of samidorphan did not produce physical or psychological dependence both in non-clinical (in rats and dogs) and in clinical studies. Accordingly, DEA finds that samidorphan does not meet the requirements for inclusion in any schedule, and should be removed from control under the CSA.

Regulatory Analyses

Executive Orders 12866, 13563, and 13771, Regulatory Planning and Review, Improving Regulation and Regulatory Review, and Reducing Regulation and Controlling Regulatory Costs

In accordance with 21 U.S.C. 811(a), this scheduling action is subject to formal rulemaking procedures done "on the record after opportunity for a hearing," which are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth the criteria for removing a drug or other substance from the list of controlled substances. Such actions are exempt from review by Office of Management and Budget (OMB) pursuant to section 3(d)(1) of Executive Order (E.O.) 12866 and the principles reaffirmed in E.O. 13563.

This final rule is not an E.O. 13771 regulatory action pursuant to E.O. 12866 and OMB guidance.\9\

\9\ Office of Mgmt. & Budget, Exec. Office of The President, Interim Guidance Implementing Section 2 of the Executive Order of January 30, 2017 Titled "Reducing Regulation and Controlling Regulatory Costs" (Feb. 2, 2017).

Executive Order 12988, Civil Justice Reform

This regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of E.O. 12988 Civil Justice Reform to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132, Federalism

This rulemaking does not have federalism implications warranting the application of E.O. 13132. The rule does not have substantial direct effects on the States, on the relationship between the Federal Government and the States, or the distribution of power and responsibilities among the various levels of government.

Executive Order 13175, Consultation and Coordination With Indian Tribal Governments

This rule does not have tribal implications warranting the application of E.O. 13175. This rule does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal Government and Indian tribes, or on the distribution of power and responsibilities between the Federal Government and Indian tribes.

Regulatory Flexibility Act

The Acting Administrator, in accordance with the Regulatory Flexibility Act (RFA) (5 U.S.C. 601-612), has reviewed this proposed rule and by approving it certifies that it will not have a significant economic impact on a substantial number of small entities. The purpose of this rule is to remove samidorphan from the list of schedules of the CSA. This action will remove regulatory controls and administrative, civil, and criminal sanctions applicable to controlled substances for handlers and proposed handlers of samidorphan. Accordingly, it has the potential for some economic impact in the form of cost savings.

If finalized, the proposed rule will affect all persons who would handle, or propose to handle samidorphan. Samidorphan is not currently available or marketed in any country. Due to the wide variety of unidentifiable and unquantifiable variables that potentially

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could influence the distribution and dispensing rates, if any, of samidorphan, DEA is unable to determine the number of entities and small entities which might handle samidorphan. In some instances where a controlled pharmaceutical drug is removed from the schedules of the CSA, DEA is able to quantify the estimated number of affected entities and small entities because the handling of the drug is expected to be limited to DEA registrants even after removal from the schedules. In such instances, DEA's knowledge of its registrant population forms the basis for estimating the number of affected entities and small entities. However, DEA does not have a basis to estimate whether samidorphan is expected to be handled by persons who hold DEA registrations, by persons who are not currently registered with DEA to handle controlled substances, or both. Therefore, DEA is unable to estimate the number of entities and small entities who plan to handle samidorphan.

Although DEA does not have a reliable basis to estimate the number of affected entities and quantify the economic impact of this final rule, a qualitative analysis indicates that this rule is likely to result in some cost savings. As noted above, DEA is specifically soliciting comments on the economic impact of this proposed rule. DEA will revise this section if warranted after consideration of any comments received. Any person planning to handle samidorphan will realize cost savings in the form of saved DEA registration fees, and the elimination of physical security, recordkeeping, and reporting requirements.

Because of these factors, DEA projects that this rule will not result in a significant economic impact on a substantial number of small entities.

Unfunded Mandates Reform Act of 1995

On the basis of information contained in the "RFA" section above, DEA has determined and certifies pursuant to the Unfunded Mandates Reform Act of 1995 (UMRA), 2 U.S.C. 1501 et seq., that this action would not result in any federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted for inflation) in any one year * * *." Therefore, neither a Small Government Agency Plan nor any other action is required under provisions of UMRA.

Paperwork Reduction Act

This action does not impose a new collection of information requirement under the Paperwork Reduction Act, 44 U.S.C. 3501-3521. This action would not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, 21 CFR part 1308 is proposed to be amended to read as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

- 1. The authority citation for 21 CFR part 1308 continues to read as follows:

  Authority: 21 U.S.C. 811, 812, 871(b), 956(b), unless otherwise noted.

- 2. In **Sec. 1308.12**, revise the introductory text of paragraph (b)(1) to read as follows:

Sec. 1308.12 Schedule II.

* * * * *

(b) * * *

(1) Opium and opiate, and any salt, compound, derivative, or preparation of opium or opiate excluding apomorphine, thebaine-derived butorphanol, dextrorphan, nalbuphine, naldemedine, nalmefene, naloxegol, naloxone, 6β-naltrexol, naltrexone, and samidorphan, and their respective salts, but including the following:

* * * * *

Timothy J. Shea,
Acting Administrator.

[FR Doc. 2020-26812 Filed 12-9-20; 8:45 am]

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*NOTICE: This is an unofficial version. An official version of this publication may be obtained directly from the **Government Publishing Office** (GPO).*

Rules - 2019

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[FR Doc No: 2019-17623]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-332]

Listing of Noroxymorphone in the Code of Federal Regulations and Assignment of a Controlled Substances Code Number

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final rule.

SUMMARY: Noroxymorphone is a derivative of opium and opiates and, as such, is a schedule II controlled substance. The Drug Enforcement Administration (DEA) has established the use of the Drug Enforcement Administration Code Number 9668 for tracking noroxymorphone and for establishing aggregate production quotas. This rule amends the Code of Federal Regulations (CFR) to reflect the current practice of using the Code Number 9668 for noroxymorphone. This rulemaking will list the schedule II controlled substance noroxymorphone as a basic class with the Code Number 9668. This rule does not affect the control of noroxymorphone as a schedule II controlled substance.

DATES: Effective: August 16, 2019.

FOR FURTHER INFORMATION CONTACT: Lynnette Wingert, Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone (202) 598-8837.

SUPPLEMENTARY INFORMATION: Noroxymorphone is a schedule II controlled substance defined in the Controlled Substances Act (CSA) by **21 U.S.C. 812**(c), Schedule II (a)(1) and 21 CFR 1308.12(b)(1), which control "opium and opiate, and any salt, compound, derivative, or preparation of opium or opiate." It meets the statutory definition of a "narcotic drug" as stated in **21 U.S.C. 802**(17) as it can be obtained from the chemical modification of substances extracted from vegetable origin, specifically from the plant species Papaver somniferum L. that is lawfully defined as "opium poppy" by 21 U.S.C. 802(19). It is not an isoquinoline alkaloid, which is categorically excluded from the statutory definition of a "narcotic drug." 21 U.S.C. 802(17)(A). Rather, noroxymorphone is a phenanthrene alkaloid with a similar chemical structure to other opium and opiate phenanthrene alkaloids listed in 21 CFR 1308.12(b)(1), such as hydrocodone, hydromorphone, dihydroetorphine, ethylmorphine, etorphine hydrochloride, metopon, thebaine, morphine, codeine, oxycodone, and oxymorphone. Noroxymorphone meets the statutory definition of "opiate" as it can be readily converted to other morphine-like substances including oxymorphone, which has an addiction-forming or addiction-sustaining abuse liability similar to morphine. Based on the similarity of the chemical structure of noroxymorphone to opium alkaloids listed in 21 CFR 1308.12(b)(1), and the fact that it is obtained by the chemical modification of these listed opium alkaloids, noroxymorphone is a derivative of opium and opiates and a schedule II controlled substance as defined by 21 U.S.C. 812(a)(1) Schedule II and 21 CFR 1308.12(b)(1).

As provided in **21 CFR 1308.03,** each controlled substance or basic class thereof is assigned a four digit Drug Enforcement Administration Controlled Substances Code Number that is used to track quantities of the controlled substance imported and exported to and from the United States. Additionally, DEA uses these Code Numbers in establishing aggregate production quotas for basic classes of controlled substances listed in schedules I and II as required by **21 U.S.C. 826.**

Since 1996, DEA has established an aggregate production quota for noroxymorphone using the DEA Controlled Substances Code Number 9668. In this final rule, DEA is amending the CFR to reflect the current practice of using the DEA Controlled Substances Code Number 9668 for noroxymorphone. Listing noroxymorphone and its DEA Controlled Substances Code Number in 21 CFR 1308.12(b)(1) does not alter the status of noroxymorphone as a Schedule II controlled substance. Noroxymorphone already is included as a Schedule II controlled substance because 21 CFR 1308.12(b)(1) controls any salt, compound, derivative, or preparation of the listed substances. Accordingly, noroxymorphone has been controlled as a derivative of the listed substances and this rule will not result in adding any new substances into the schedules. Listing noroxymorphone also will not affect the aggregate production quota currently established. DEA-registered manufacturers of noroxymorphone previously granted individual quotas for such purposes may continue to apply for quota after this rule is finalized.

Regulatory Analyses

Administrative Procedure Act (APA)

Under 5 U.S.C. 553(b)(3)(B), an agency may dispense with notice and comment rulemaking when, for good cause, it "finds . . . that notice and public procedure thereon are impracticable, unnecessary, or contrary to the public interest." DEA finds that notice and comment rulemaking is unnecessary and that good cause exists to dispense with these procedures because the inclusion of noroxymorphone and its DEA Controlled Substances Code Number in the list of schedule II substances in 21 CFR 1308.12(b)(1) is " 'a minor or merely technical amendment in which the public is not particularly interested.' " National Nutritional Foods Ass'n v. Kennedy, 572 F.2d 377, 385 (2d Cir. 1978) (quoting S. Rep. No. 79-752, at 200 (1945)). See also Utility Solid Waste Activities Group v. E.P.A., 236 F.3d 749, 755 (D.C. Cir. 2001) (the "unnecessary" prong "is confined to those situations in which the administrative rule is a routine determination, insignificant in nature and impact, and inconsequential to the industry and public") (int. quotations and citation omitted). This rule is a "technical amendment" to 21 CFR 1308.12(b)(1) as it is "insignificant in nature and impact, and inconsequential to the industry and public."

Similarly, the APA states that a rule cannot be made effective less than 30 days after publication, unless the rule falls under one of three enumerated exceptions. One of these exceptions is when an agency provides good cause that compliance would be impracticable, unnecessary, or contrary to the public interest. 5 U.S.C. 553(d)(3). A delayed effective date for this rule is unnecessary because this rule simply lists the schedule II controlled substance noroxymorphone in 21 CFR 1308.12(b)(1) as a basic class and assigns to it the DEA Controlled Substances Code Number 9668. This rule merely amends the CFR to reflect the current DEA business practice and better assist companies in complying with registration and quota requirements. In addition, this rule does not require those firms that handle

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noroxymorphone to alter their current practices with respect to their quota applications and reporting obligations.

For the reasons stated above, notice and comment procedures are unnecessary and this rule may be made effective upon publication.

Executive Order 12866, 13563, and 13771, Regulatory Planning and Review, Improving Regulation and Regulatory Review, and Reducing Regulation and Controlling Regulatory Costs

This regulation has been drafted and reviewed in accordance with the principles of Executive Orders 12866 and 13563. This rule is not a significant regulatory action under Executive Order 12866. Noroxymorphone is a derivative of opium and opiates and, as such, is a schedule II controlled substance. In this final rule, DEA is merely amending its regulations to reflect the current practice of using the DEA Controlled Substances Code Number 9668 for noroxymorphone. Listing noroxymorphone and its DEA Controlled Substances Code Number will not alter the status of noroxymorphone as a Schedule II controlled substance. Accordingly, this rule has not been reviewed by the Office of Management and Budget.

Because this final rule is not significant under Executive Order 12866, it is not subject to the requirements of Executive Order 13771.\1\

\1\ Office of Mgmt. & Budget, Exec. Office of The President, Interim Guidance Implementing Section 2 of the Executive Order of January 30, 2017 Titled "Reducing Regulation and Controlling Regulatory Costs" (Feb. 2, 2017).

Executive Order 12988, Civil Justice Reform

This regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of Executive Order 12988 to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132, Federalism

This rulemaking does not have federalism implications warranting the application of Executive Order 13132. The rule does not have substantial direct effects on the States, on the relationship between the national government and the States, or the distribution of power and responsibilities among the various levels of government.

Executive Order 13175, Consultation and Coordination With Indian Tribal Governments

This rule does not have tribal implications warranting the application of Executive Order 13175. It does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal Government and Indian tribes, or on the distribution of power and responsibilities between the Federal Government and Indian tribes.

Regulatory Flexibility Act

The Regulatory Flexibility Act (RFA) (5 U.S.C. 601-612) applies to rules that are subject to notice and comment under section 553(b) of the APA or other laws. As explained above, the DEA determined that there was good cause to exempt this final rule from notice and comment. Consequently, the RFA does not apply to this final rule.

Unfunded Mandates Reform Act of 1995

This final rule will not result in the expenditure by state, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted for inflation) in any one year, and will not significantly or uniquely affect small governments. Therefore, no actions were deemed under the provisions of the Unfunded Mandates Reform Act of 1995, 2 U.S.C. 1532.

Paperwork Reduction Act of 1995

This rule does not impose a collection of information requirement under the Paperwork Reduction Act of 1995. 44 U.S.C. 3501-3521.

Congressional Review Act

This rule is not a major rule as defined by section 804 of the Congressional Review Act (CRA), 5 U.S.C. 804. Pursuant to the CRA, the DEA is submitting a copy of this final rule to both Houses of Congress and to the Comptroller General.

List of Subjects in 21 CFR Part 1308

Drug traffic control, Controlled Substances.

For the reasons set out above, 21 CFR part 1308 is amended as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

- 1. The authority citation for part 1308 continues to read as follows:

  Authority: 21 U.S.C. 811, 812, 871(b), unless otherwise noted.

- 2. Section 1308.12 is amended by redesignating paragraphs (b)(1)(x) through (xviii) as paragraphs (b)(1)(xi) through (xix), respectively, and by adding a new paragraph (b)(1)(x) to read as follows:

Sec. 1308.12 **Schedule II.**

* * * * *

(b) * * *

(1) * * *

* * * * *

(x) Noroxymorphone	9668

* * * * *

Dated: August 5, 2019.

Uttam Dhillon,
Acting Administrator.

[FR Doc. 2019-17623 Filed 8-15-19; 8:45 am]

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Rules - 2020

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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-715]

Schedules of Controlled Substances: Placement of Oliceridine in Schedule II

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Interim final rule, with request for comments.

SUMMARY: On August 7, 2020, the U.S. Food and Drug Administration approved a new drug application for oliceridine, chemically known as *N*-[(3-methoxythiophen-2-yl)methyl] ({2-[(9*R*)-9-(pyridin-2-yl)-6-oxaspiro [4.5]decan-9-yl]ethyl{time})amine fumarate. The Department of Health and Human Services provided the Drug Enforcement Administration (DEA) with a scheduling recommendation to place oliceridine in schedule II of the Controlled Substances Act (CSA). In accordance with the CSA, as revised by the Improving Regulatory Transparency for New Medical Therapies Act, DEA is hereby issuing an interim final rule placing oliceridine, including its isomers, esters, ethers, salts and salts of isomers, esters and ethers whenever the existence of such isomers, esters, ethers and salts is possible, in schedule II of the CSA.

DATES: The effective date of this rulemaking is October 30, 2020. Interested persons may file written comments on this rulemaking in accordance with **21 U.S.C. 811**(j)(3) and **21 CFR 1308.43**(g). Electronic comments must be submitted, and written comments must be postmarked, on or before November 30, 2020. Commenters should be aware that the electronic Federal Docket Management System will not accept comments after 11:59 p.m. Eastern Time on the last day of the comment period.

Interested persons may file a request for hearing or waiver of hearing in accordance with **21 U.S.C. 811**(j)(3) and **21 CFR 1308.44**. Requests for hearing and waivers of an opportunity for a hearing or to participate in a hearing must be received on or before November 30, 2020.

ADDRESSES: To ensure proper handling of comments, please reference "Docket No. DEA-715" on all correspondence, including any attachments.

- *Electronic comments:* The Drug Enforcement Administration encourages that all comments be submitted electronically through the Federal eRulemaking Portal, which provides the ability to type short comments directly into the comment field on the web page or attach a file for lengthier comments. Please go to http://www.regulations.gov and follow the online instructions at that site for submitting comments. Upon completion of your submission, you will receive a Comment Tracking Number for your comment. Please be aware that submitted comments are not instantaneously available for public view on Regulations.gov. If you have received a Comment Tracking Number, your comment has been successfully submitted and there is no need to resubmit the same comment.
- *Paper comments:* Paper comments that duplicate the electronic submission are not necessary and are discouraged. Should you wish to mail a paper comment in lieu of an electronic comment, it should be sent via regular or express mail to: Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrissette Drive, Springfield, VA 22152.
- *Hearing requests:* All requests for hearing and waivers of participation must be sent to: Drug Enforcement Administration, Attn: Administrator, 8701 Morrissette Drive, Springfield, Virginia 22152. All requests for hearing and waivers of participation should also be sent to: (1) Drug Enforcement Administration, Attn: Hearing Clerk/LJ, 8701 Morrissette Drive, Springfield, Virginia 22152; and (2) Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrissette Drive, Springfield, Virginia 22152.

FOR FURTHER INFORMATION CONTACT: Scott A. Brinks, Regulatory Drafting and Policy Support Section, Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (571) 362-3261.

SUPPLEMENTARY INFORMATION:

Posting of Public Comments

Please note that all comments received are considered part of the public record. They will, unless reasonable cause is given, be made available by the Drug Enforcement Administration (DEA) for public inspection online at http://www.regulations.gov. Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter. The Freedom of Information Act applies to all comments received. If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want it to be made publicly available, you must include the phrase "PERSONAL IDENTIFYING INFORMATION" in the first paragraph of your comment. You must also place all of the personal identifying information you do not want made publicly available in the first paragraph of your comment and identify what information you want redacted.

If you want to submit confidential business information as part of your comment, but do not want it to be made publicly available, you must include the phrase "CONFIDENTIAL BUSINESS INFORMATION" in the first paragraph of your comment. You must also prominently identify the confidential business information to be redacted within the comment.

Comments containing personal identifying information and confidential business information identified as directed above will generally be made publicly available in redacted form. If a comment has so much confidential business information or personal identifying information that it cannot be effectively redacted, all or part of that comment may not be made publicly available. Comments posted to http://www.regulations.gov may include any personal identifying information (such as name, address, and phone number) included in the text of your electronic submission that is not identified as directed above as confidential.

An electronic copy of this document and supplemental information, including the complete Department of Health and Human Services (HHS) and DEA eight-factor analyses, to this interim final rule (IFR) are available at http://www.regulations.gov for easy reference.

Request for Hearing or Appearance; Waiver

Pursuant to **21 U.S.C. 811**(a), this action is a formal rulemaking "on the record after opportunity for a hearing." Such proceedings are conducted pursuant to the provisions of the Administrative Procedure Act (APA), 5 U.S.C. 551-559. **21 CFR 1308.41-1308.45**; **21 CFR part 1316**, subpart D. Interested persons may file

requests for a hearing or notices of intent to participate in a hearing in conformity with the requirements of **21 CFR 1308.44** (a) or (b), and include a statement of interest in the proceeding and the objections or issues, if any, concerning which the person desires to be heard. Any interested person may file a waiver of an opportunity for a hearing or to participate in a hearing together with a written statement regarding the interested person's position on the

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matters of fact and law involved in any hearing as set forth in **21 CFR 1308.44(c)**.

All requests for a hearing and waivers of participation must be sent to DEA using the address information provided above.

Background and Legal Authority

Under the Improving Regulatory Transparency for New Medical Therapies Act, Public Law 114-89, 2(b), 129 Stat. 698, 700 (2015), DEA is required to commence an expedited scheduling action with respect to certain new drugs approved by the U.S. Food and Drug Administration (FDA). As provided in **21 U.S.C. 811(j)**, this expedited scheduling is required where both of the following conditions apply: (1) The Secretary of the Department of Health and Human Services (the Secretary) has advised DEA that an application for a new drug has been submitted for a drug that has a stimulant, depressant, or hallucinogenic effect on the central nervous system, and that it appears that such drug has an abuse potential; and, (2) the Secretary recommends that DEA control the drug in schedule II, III, IV, or V pursuant to **21 U.S.C. 811(a)** and (b). In these circumstances, DEA is required to issue an IFR controlling the drug within 90 days.

The law further states that the 90-day timeframe starts the later of (1) the date DEA receives the HHS scientific and medical evaluation/scheduling recommendation, or (2) the date DEA receives notice of the application approval by HHS. In addition, the law specifies that the rulemaking shall become immediately effective as an IFR without requiring DEA to demonstrate good cause therefor. Thus, the purpose of subsection (j) is to speed the process by which DEA schedules newly approved drugs that are currently either in schedule I or not controlled (but which have sufficient abuse potential to warrant control) so that such drugs may be marketed without undue delay following FDA approval.\1\

\1\ Given the parameters of subsection (j), in DEA's view, it would not apply to a reformulation of a drug containing a substance currently in schedules II through V for which an NDA has recently been approved.

Subsection (j) further provides that the IFR shall give interested persons the opportunity to comment and to request a hearing. After the conclusion of such proceedings, DEA must issue a final rule in accordance with the scheduling criteria of subsections **21 U.S.C. 811(b)**, (c), and (d) and **21 U.S.C. 812(b)**.

On November 2, 2017, Trevena, Inc. (Sponsor) submitted an initial New Drug Application (NDA) to FDA for oliceridine that was subsequently resubmitted on February 7, 2020. FDA determined that oliceridine is a new molecular entity, and HHS determined that oliceridine has a depressant effect on the central nervous system. On August 7, 2020, FDA approved the NDA for oliceridine for medical use as an intravenous drug for the management of acute pain severe enough to require an intravenous opioid analgesic and for patients for whom alternative treatments are inadequate.

Determination To Schedule Oliceridine

On July 27, 2020, DEA received a scientific and medical evaluation document from HHS prepared by FDA related to oliceridine, titled: "Basis for the Recommendation to Control Oliceridine and its Salts in Schedule II of the Controlled Substances Act." Pursuant to **21 U.S.C. 811(b)**, this document contained an eight-factor analysis of the abuse potential of oliceridine, along with HHS's recommendation to control oliceridine under schedule II of the CSA. Subsequently, on August 7, 2020, DEA received notification from HHS that FDA had approved an NDA for oliceridine (OLINVYK).

In response, DEA reviewed the scientific and medical evaluation and scheduling recommendation provided by HHS, along with all other relevant data, and completed its own eight-factor review document pursuant to **21 U.S.C. 811(c)**. DEA concluded that oliceridine met the **21 U.S.C. 812(b)(2)** criteria for placement in schedule II of the CSA.

Pursuant to **subsection 811(j)**, and based on HHS's recommendation, the NDA approval by HHS/FDA, and DEA's determination, DEA is issuing this IFR to schedule oliceridine as a schedule II controlled substance under the CSA.

Included below is a brief summary of each factor as analyzed by HHS and DEA, and as considered by DEA in its scheduling action. Please note that both the DEA and HHS analyses are available in their entirety under "Supporting Documents" in the public docket for this IFR at http://www.regulations.gov, under Docket Number "DEA-715." Full analysis of, and citations to, the information referenced in the summary may also be found in the supporting and related material.

1. *Its Actual or Relative Potential for Abuse:* Oliceridine is a new molecular entity that has not been marketed in the United States or any other country. Thus, information about the diversion and actual abuse of oliceridine is limited. Oliceridine is currently not available for medical treatment, has not been diverted from legitimate sources, and individuals have not taken this substance in amounts sufficient to create a hazard to public health and safety. DEA notes that there are no reports for oliceridine in the National Forensic Laboratory Information System (NFLIS),\2\ which collects drug identification results from drug cases submitted to and analyzed by Federal, State, and local forensic laboratories. There were also no reports in DEA's laboratory drug evidence data system of record, STARLiMS.\3\

\2\ NFLIS represents an important resource in monitoring illicit drug trafficking, including the diversion of legally manufactured pharmaceuticals into illegal markets. NFLIS is a comprehensive information system that includes data from forensic laboratories that handle more than 96 percent of an estimated 1.0 million distinct annual State and local drug analysis cases. NFLIS includes drug chemistry results from completed analyses only. While NFLIS data is not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. See 76 FR 77330, 77332 (Dec. 12, 2011). NFLIS data were queried on July 28, 2020.

\3\ On October 1, 2014, DEA implemented STARLIMS (a web-based, commercial laboratory information management system) to replace the System to Retrieve Information from Drug Evidence (STRIDE) as its laboratory drug evidence data system of record. DEA laboratory data submitted after September 30, 2014, are reposited in STARLIMS. STARLIMS data were queried on July 28, 2020.

According to the legislative history of the CSA, one of the criteria by which DEA should assess actual or relative potential for abuse is whether the substance in question "is so related in its action to a substance already listed as having a potential for abuse to make it likely that it will have the same potential for abuse as such substance, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community." \4\ As stated by HHS, oliceridine is a high-affinity mu opioid agonist that produces behavioral effects similar to other mu opioid agonists, such as the schedule II opioid morphine. Moreover, in a rat drug discrimination study, oliceridine generalized to morphine, showing that oliceridine has opioid-like properties. In a clinical study investigating the abuse potential of oliceridine, HHS concluded that oliceridine produced subjective responses that were similar to those for morphine. Specifically, like morphine, oliceridine produced positive subjective responses and euphoria-related adverse events in clinical studies. Together, this

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evidence demonstrates that oliceridine is related in action and effect to the schedule II substance morphine, and can therefore be expected to have a similar potential for abuse.

\4\ Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970), reprinted in U.S.C.C.A.N. 4566, 4603.

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2. *Scientific Evidence of Its Pharmacological Effects, if Known:* Oliceridine has high affinity for the mu-opioid receptor and does not bind to any other receptors that are typically associated with abuse, such as kappa and delta opioid receptors, cannabinoid receptors, GABAergic receptors, or other ion channels. According to HHS, general behavioral studies in animals indicate that oliceridine produces behavioral and motor effects similar to those of morphine, a schedule II substance. Additionally, oliceridine produces self-administration in rats. Furthermore, in a drug discrimination study used to predict subjective effects in humans, oliceridine mimicked the stimulus effects of morphine. In a human abuse potential (HAP) study, therapeutic and supratherapeutic doses of oliceridine produced euphoria, somnolence, and paresthesia. These adverse events are consistent with those of other schedule II opioids such as morphine. In other clinical studies, adverse events such as somnolence, sedation, anxiety, restlessness, and paresthesia were seen in subjects treated with oliceridine. As concluded by HHS, results from preclinical and clinical studies indicate that oliceridine has abuse potential similar to morphine.

3. *The State of Current Scientific Knowledge Regarding the Drug or Other Substance:* Oliceridine is a new molecular entity, chemically known as *N*-[(3-methoxythiophen-2-yl)methyl] ({2-[(9*R*)-9-(pyridin-2-yl)-6-oxaspiro [4.5]decan-9-yl]ethyl{time})amine fumarate. It has a molecular formula of $C_{22}H_{30}N_2O_2S.C_4H_4O_4$. Oliceridine is a white to lightly-colored solid that is sparingly soluble in water. On August 7, 2020, FDA approved an NDA for oliceridine for medical use to manage acute pain severe enough to require an intravenous opioid analgesic and for which alternative treatments are inadequate. Thus, oliceridine has an accepted medical use in the United States. Oliceridine will be marketed as an intravenous medication formulated in vials containing 1, 2, or 30 mg of oliceridine.

4. *Its History and Current Pattern of Abuse:* There is no information available relating to the history and current pattern of abuse of oliceridine, since this drug is not currently marketed in any country. HHS notes that oliceridine produces abuse-related signals, such as euphoria and somnolence, and abuse potential similar to that of schedule II controlled substance morphine. DEA searched NFLIS and STARLiMS databases for oliceridine encounters. Consistent with the fact that oliceridine is a new molecular entity, these databases had no records of encounters of oliceridine by law enforcement.

5. *The Scope, Duration, and Significance of Abuse:* Oliceridine is currently not marketed in any country. Thus, information on the scope, duration, and significance of abuse for oliceridine is lacking. However, as stated by HHS, data from animal and human studies indicate that oliceridine has abuse potential similar to morphine. Therefore, upon marketing, oliceridine scope of abuse is expected to be similar to morphine.

6. *What, if any, Risk There is to the Public Health:* The extent of abuse potential of a drug is an indication of its public health risk. Data from the preclinical and clinical studies suggest that the abuse potential and physical or psychological dependence potential of oliceridine are similar to the schedule II substance morphine. Thus, oliceridine upon its availability for marketing would be expected to create a public health risk.

7. *Its Psychic or Physiological Dependence Liability:* Physical dependence for oliceridine was tested in an animal toxicity study. According to HHS, the animal toxicity study using rats demonstrated dose-dependent decreases in food consumption and body weight as well as classic opioid withdrawal signs from discontinuation of oliceridine. In a rat self-administration study as well as in clinical studies, oliceridine produced rewarding effects similar to morphine. Based on these studies, HHS stated that oliceridine may produce physical and psychological dependence.

8. *Whether the Substance is an Immediate Precursor of a Substance Already Controlled under the CSA:* Oliceridine is not an immediate precursor of any controlled substance, as defined in **21 U.S.C. 802**(23).

Conclusion: After considering the scientific and medical evaluation conducted by HHS, HHS's scheduling recommendation, and its own eight-factor analysis, DEA has determined that these facts and all relevant data constitute substantial evidence of a potential for abuse of oliceridine. As such, DEA hereby schedules oliceridine as a controlled substance under the CSA.

Determination of Appropriate Schedule

The CSA outlines the findings required to place a drug or other substance in any particular schedule (I, II, III, IV, or V). **21 U.S.C. 812**(b). After consideration of the analysis and recommendation of the Assistant Secretary for Health of HHS and review of all available data, the Acting Administrator of DEA, pursuant to 21 U.S.C. 812(b)(2), finds that:

1. Oliceridine Has a High Potential for Abuse

Oliceridine is a mu-opioid receptor agonist and produces behavioral effects that are similar to those of morphine (schedule II opioid substance) in animals and humans. A self-administration study in animals demonstrated that oliceridine produced self-administration that was comparable to morphine. Additionally, a drug-discrimination study in animals demonstrated that oliceridine generalized to morphine, indicating that it has mu-opioid receptor agonist properties. Results from a HAP study showed that oliceridine produces positive subjective effects as well as adverse events such as euphoria, similar to that of morphine, a schedule II substance with a high potential for abuse. Lastly, clinical studies in healthy individuals indicate that oliceridine produces abuse-related adverse events such as euphoria and sedation. These data collectively indicate that oliceridine has a high potential for abuse similar to the schedule II substance morphine.

2. Oliceridine Has a Currently Accepted Medical Use in the United States

FDA recently approved a NDA for oliceridine for the management of acute pain severe enough to require an intravenous opioid analgesic and for patients for whom alternative treatments are inadequate. Thus, oliceridine has a currently accepted medical use in treatment in the United States.

3. Abuse of Oliceridine May Lead To Severe Psychological or Physical Dependence

Chronic administration of oliceridine in rats followed by drug discontinuation produced classic opioid withdrawal signs, similar to that of schedule II drug morphine. This study would indicate oliceridine's potential to cause physical dependence similar to that of morphine. Oliceridine also produces self-administration in rats and positive subjective responses in a HAP study. These results parallel those produced by morphine and suggest that oliceridine can also produce psychological dependence. These data collectively suggest that oliceridine abuse may lead to psychological and physical

[[Page 68752]]

dependence similar to that of schedule II opioids.

Based on these findings, the Acting Administrator of DEA concludes that oliceridine warrants control in schedule II of the CSA. **21 U.S.C. 812**(b)(2).

Requirements for Handling Oliceridine

Oliceridine is subject to the CSA's schedule II regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, reverse distribution, dispensing, importing, exporting, research, and conduct of instructional activities and chemical analysis with, and possession involving schedule II substances, including the following:

1. *Registration.* Any person who handles (manufactures, distributes, reverse distributes, dispenses, imports, exports, engages in research, or conducts instructional activities or chemical analysis with, or possesses) oliceridine, or who desires to handle oliceridine, must be registered with DEA to conduct such activities pursuant to **21 U.S.C. 822, 823, 957,** and **958** and in accordance with **21 CFR parts 1301** and **1312.** Any person who currently handles or intends to handle oliceridine, and is not registered with DEA, must submit an application for registration and may not continue to handle oliceridine, unless DEA has approved the application for registration, pursuant to 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312.

2. *Quota.* Only registered manufacturers are permitted to manufacture oliceridine in accordance with a quota assigned pursuant to **21 U.S.C. 826** and in accordance with **21 CFR part 1303.**

3. *Disposal of stocks.* Any person who does not desire or is not able to maintain a schedule II registration must surrender all quantities of currently held oliceridine, or may transfer all quantities of currently held oliceridine to a person registered with DEA in accordance with **21 CFR part 1317,** in addition to all other applicable Federal, State, local, and tribal laws.

4. *Security.* Oliceridine is subject to schedule II security requirements and must be handled and stored pursuant to **21 U.S.C. 821** and **823** and in accordance with **21 CFR 1301.71-1301.93.**

5. *Labeling and Packaging.* All labels, labeling, and packaging for commercial containers of oliceridine must comply with **21 U.S.C. 825** and **958**(e) and be in accordance with **21 CFR part 1302.**

6. *Inventory.* Every DEA registrant who possesses any quantity of oliceridine must take an inventory of oliceridine on hand, pursuant to **21 U.S.C. 827** and **958**(e), and in accordance with **21 CFR 1304.03, 1304.04,** and **1304.11.**

Any person who becomes registered with DEA to handle oliceridine must take an initial inventory of all stocks of controlled substances containing oliceridine on hand on the date the registrant first engages in the handling of controlled substances, pursuant to **21 U.S.C. 827** and **958**(e), and in accordance with **21 CFR 1304.03, 1304.04,** and **1304.11.**

After the initial inventory, every DEA registrant must take a new inventory of all stocks of controlled substances (including oliceridine) on hand every two years, pursuant to **21 U.S.C. 827** and **958**(e), and in accordance with **21 CFR 1304.03, 1304.04,** and **1304.11.**

7. *Records and Reports.* Every DEA registrant must maintain records and submit reports for oliceridine, pursuant to **21 U.S.C. 827** and **958**(e), and in accordance with **21 CFR parts 1304, 1312,** and **1317.**

8. *Orders for oliceridine.* Every DEA registrant who distributes oliceridine is required to comply with order form requirements, pursuant to **21 U.S.C. 828,** and in accordance with **21 CFR part 1305.**

9. *Prescriptions.* All prescriptions for oliceridine or products containing oliceridine must comply with **21 U.S.C. 829,** and be issued in accordance with **21 CFR parts 1306** and **1311,** subpart C.

10. *Manufacturing and Distributing.* In addition to the general requirements of the CSA and DEA regulations that are applicable to manufacturers and distributors of schedule II controlled substances, such registrants should be advised that (consistent with the foregoing considerations) any manufacturing or distribution of oliceridine may only be for the legitimate purposes consistent with the drug's labeling, or for research activities authorized by the Federal Food, Drug, and Cosmetic Act, as applicable, and the CSA.

11. *Importation and Exportation.* All importation and exportation of oliceridine must be in compliance with **21 U.S.C. 952, 953, 957,** and **958,** and in accordance with **21 CFR part 1312.**

12. *Liability.* Any activity involving oliceridine not authorized by, or in violation of, the CSA or its implementing regulations, is unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

Regulatory Analyses

Administrative Procedure Act

Public Law 114-89 was signed into law, amending **21 U.S.C. 811**. This amendment provides that in cases where a new drug is (1) approved by HHS, and (2) HHS recommends control in CSA schedule II-V, DEA shall issue an IFR scheduling the drug within 90 days. Additionally, the law specifies that the rulemaking shall become immediately effective as an IFR without requiring DEA to demonstrate good cause. Therefore, DEA has determined that the notice and comment requirements of section 553 of the APA, 5 U.S.C. 553, do not apply to this scheduling action.

Executive Orders 12866, 13563, and 13771, Regulatory Planning and Review, Improving Regulation and Regulatory Review, and Reducing Regulation and Controlling Regulatory Costs

In accordance with **21 U.S.C. 811**(a) and (j), this scheduling action is subject to formal rulemaking procedures performed "on the record after opportunity for a hearing," which are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth the procedures and criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget (OMB) pursuant to section 3(d)(1) of Executive Order (E.O.) 12866 and the principles reaffirmed in E.O. 13563.

This IFR is not an E.O. 13771 regulatory action pursuant to E.O. 12866 and OMB guidance.\5\

\5\ Office of Management and Budget, Executive Office of The President, Interim Guidance Implementing Section 2 of the Executive Order of January 30, 2017, Titled "Reducing Regulation and Controlling Regulatory Costs" (Feb. 2, 2017).

Executive Order 12988, Civil Justice Reform

This regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of E.O. 12988 to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132, Federalism

This rulemaking does not have federalism implications warranting the application of E.O. 13132. The rule does not have substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government.

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Executive Order 13175, Consultation and Coordination With Indian Tribal Governments

This rule does not have tribal implications warranting the application of E.O. 13175. It does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal government and Indian tribes, or on the distribution of power and responsibilities between the Federal government and Indian tribes.

Regulatory Flexibility Act

The Regulatory Flexibility Act (RFA) (5 U.S.C. 601-612) applies to rules that are subject to notice and comment under section 553(b) of the APA. Under **21 U.S.C. 811**(j), DEA is not required to publish a general notice of proposed rulemaking. Consequently, the RFA does not apply to this IFR.

Unfunded Mandates Reform Act of 1995

In accordance with the Unfunded Mandates Reform Act (UMRA) of 1995, 2 U.S.C. 1501 et seq., DEA has determined that this action would not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million or more (adjusted for inflation) in any one year." Therefore, neither a Small Government Agency Plan nor any other action is required under UMRA of 1995.

Paperwork Reduction Act of 1995

This action does not impose a new collection of information requirement under the Paperwork Reduction Act of 1995. 44 U.S.C. 3501-3521. This action does not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Congressional Review Act

This rule is not a major rule as defined by the Congressional Review Act (CRA), 5 U.S.C. 804. This rule does not result in: An annual effect on the economy of $100 million or more; a major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; or significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of U.S.-based companies to compete with foreign based companies in domestic and export markets. However, pursuant to the CRA, DEA has submitted a copy of this IFR to both Houses of Congress and to the Comptroller General.

List of Subjects

21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, DEA amends 21 CFR part 1308 as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

- 1. The authority citation for 21 CFR part 1308 continues to read as follows:

  Authority: 21 U.S.C. 811, 812, 871(b), **956**(b), unless otherwise noted.

- 2. Amend **Sec. 1308.12** by:
- a. Redesignating paragraph (c)(18) through (c)(29) as (c)(19) through (c)(30);
- b. Adding new paragraph (c)(18).

The addition to read as follows:

Sec. 1308.12 Schedule II.

* * * * *

(c) * * *

(18) Oliceridine (*N*-[(3-methoxythiophen-2-yl)methyl] ({2-[(9*R*)-9-(pyridin-2-yl)-6-oxaspiro [4.5]decan-9-yl]ethyl})amine fumarate)	9245

* * * * *

Timothy J. Shea,
Acting Administrator.

[FR Doc. 2020-22762 Filed 10-29-20; 8:45 am]

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Rules - 2019

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[Rules and Regulations]
[Pages 2448-2449]
From the Federal Register Online via the Government Publishing Office [www.gpo.gov]
[FR Doc No: 2019-01470]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-305]

Control of Immediate Precursor Used in the Illicit Manufacture of Fentanyl as Schedule II Controlled Substances; Correction

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final rule.

SUMMARY: On June 29, 2010, the Drug Enforcement Administration (DEA) placed the fentanyl immediate precursor chemical "4-anilino-N-phenethyl-4-piperidine," (CASRN 21409-26-7) into Schedule II of the Controlled Substances Act. It has come to DEA's attention that the drug name listed in the final rule contained a minor error and the drug name should have been "4-anilino-N-phenethylpiperidine (ANPP)." This document corrects that listing in the Code of Federal Regulations. Because this change is ministerial, the DEA has determined for good cause that public notice and comment is unnecessary under the Administrative Procedure Act (APA) and is implementing this change by means of a final rule without notice and comment.

DATES: Effective February 7, 2019.

FOR FURTHER INFORMATION CONTACT: Kathy L. Federico, Regulatory Drafting Section, Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (202) 598-6812.

SUPPLEMENTARY INFORMATION: On June 29, 2010, the DEA designated ANPP as an immediate precursor for the Schedule II controlled substance fentanyl under the definition set forth in **21 U.S.C. 802**(23). 75 FR 37295 (Jun. 29, 2010). ANPP is the immediate chemical intermediary in the synthesis process used by clandestine laboratory operators for the illicit manufacture of the Schedule II controlled substance fentanyl.

In the rulemaking, the DEA inadvertently introduced an error into the drug name. This rulemaking is intended to correct that ministerial error.

Both the notice of proposed rulemaking and the final rule referenced the chemical name as "4-anilino-N-phenethyl-4-piperidine (ANPP)" and "CASRN 21409-26-7" (Chemical Abstract Service Registry Number).\1\ 73 FR 19175, 19176 (Apr. 9, 2008); 75 FR 37295, 37296 (Jun. 29, 2010). While the abbreviation ANPP and the Chemical Abstract Service Registry Number 21409-26-7 correctly identified the compound, the name "4-anilino-N-phenethyl-4-piperidine" is incorrect and is without meaning. The correct

[[Page 2449]]

name is "4-anilino-N-phenethylpiperidine".

\1\ Chemical Abstract Service Registry Numbers are used to identify specific compounds. Chemicals are often identified by a wide variety of names, which are generated according to international/regional naming conventions relating to chemical formula and chemical structure. Chemical Abstract Service Registry Numbers link a specific chemical compound across various nomenclatures (naming schemes) and are useful in definitively identifying a particular compound. Synonymous names are under one CASRN number.

There is no existing chemical compound named "4-anilino-N-phenethyl-4-piperidine." While chemists understood which compound was being controlled by the DEA due to the abbreviation ANPP and specific CASRN number, DEA is now correcting the listing in the Code of Federal Regulations (CFR) by revising 21 CFR 1308.12 to provide the correct name.

Administrative Procedure Act

The Administrative Procedure Act (APA) generally requires that agencies, prior to issuing a new rule, publish a notice of proposed rulemaking in the Federal Register. The APA also provides, however, that agencies may be exempt from this requirement when "the agency for good cause finds (and incorporates the finding and a brief statement of reasons therefore in the rules issued) that notice and public procedure thereon are impracticable, unnecessary, or contrary to the public interest." \2\

\2\ 5 U.S.C. 553(b)(B).

The name "4-anilino-N-phenethyl-4-piperidine" is without meaning and no substance exists by that chemical name. The inclusion of the "-4" in the middle of the name is nonsensical. Because the correct Chemical Abstract Service Registry Number and abbreviation "ANPP" were given in the original rulemaking, chemists have understood which compound has been (and remains) controlled by DEA. There is no change as to what substance is controlled. Public notice and comment is thus unnecessary.

For the same reasons that the DEA has determined that public notice and comment is unnecessary, the DEA also finds good cause to adopt an effective date that would be less than 30 days after the publication in the Federal Register pursuant to the APA. 5 U.S.C. 553(d). Accordingly, this amendment will be effective as of the date of publication in the Federal Register.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, 21 CFR part 1308 is amended as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

- 1. The authority citation for part 1308 continues to read as follows:

  Authority: 21 U.S.C. 811, 812, **871**(b), **956**(b), unless otherwise noted.

- 2. Section 1308.12 is amended by revising paragraph (g)(3) to read as follows:

Sec. 1308.12 **Schedule II.**

* * * * *

(g) * * *

(3) Immediate precursor to fentanyl:

(i) 4-anilino-N-phenethylpiperidine (ANPP)	8333

(ii) [Reserved]

Dated: December 14, 2018.

Uttam Dhillon,
Acting Administrator.

[FR Doc. 2019-01470 Filed 2-6-19; 8:45 am]

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Rules - 2020

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[Rules and Regulations]
[Pages 21320-21325]
From the Federal Register Online via the Government Publishing Office [www.gpo.gov]
[FR Doc No: 2020-07381]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-496]

Control of the Immediate Precursor Norfentanyl Used in the Illicit Manufacture of Fentanyl as a Schedule II Controlled Substance

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final rule.

SUMMARY: The Drug Enforcement Administration (DEA) is designating the precursor chemical, N-phenyl-N-(piperidin-4-yl)propionamide (norfentanyl) as an immediate precursor for the schedule II controlled substance fentanyl. Furthermore, DEA is finalizing the control of norfentanyl as a schedule II substance under the Controlled Substances Act (CSA).

DATES: This rulemaking becomes effective May 18, 2020.

FOR FURTHER INFORMATION CONTACT: Scott A. Brinks, Regulatory Drafting and Policy Support Section (DPW), Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (571) 362-3261.

SUPPLEMENTARY INFORMATION: Norfentanyl is the immediate chemical intermediary in a synthesis process currently used by clandestine laboratory operators for the illicit manufacture of the schedule II controlled substance fentanyl. The distribution of illicitly manufactured fentanyl has caused an unprecedented outbreak of thousands of fentanyl-related overdoses in the United States in recent years. DEA believes that the control of norfentanyl as a schedule II controlled substance is necessary to prevent its diversion as an immediate chemical intermediary for the illicit manufacture of fentanyl.

DEA is extremely concerned with the recent increase in the illicit manufacture and distribution of fentanyl. Therefore, on September 17, 2019, DEA published a Notice of Proposed Rulemaking (NPRM) to designate the precursor chemical, N-phenyl-N-(piperidin-4-yl)propionamide (norfentanyl), as an immediate precursor of the schedule II controlled substance fentanyl under the definition set forth in **21 U.S.C. 802**(23), and to control it as a schedule II substance under the CSA. 84 FR 48815. This rulemaking finalizes that NPRM.

Legal Authority

Under 21 U.S.C. 811(e), the Attorney General may place an immediate precursor into the same schedule as the controlled substance that the immediate precursor is used to make, if the substance meets the requirements of an immediate precursor under **21 U.S.C. 802**(23).

Background

The DEA is extremely concerned with the increase in the illicit manufacture and distribution of fentanyl abroad. Fentanyl is a synthetic opioid and was first synthesized in Belgium in the late 1950's. Fentanyl is controlled in schedule II of the CSA due to its high potential for abuse and dependence, and accepted medical use in treatment in the United States. Fentanyl was introduced into medical practice and is approved in the United States for anesthesia and analgesia. However, due to its pharmacological effects, fentanyl can serve as a substitute for heroin, oxycodone, and other opioids in opioid dependent individuals. The trafficking of fentanyl in the United States continues to pose an imminent hazard to the public safety. Since 2012, fentanyl has shown a dramatic increase in the illicit drug supply as a single substance, in mixtures with other illicit drugs (i.e. heroin, cocaine, and methamphetamine), or in forms that mimic pharmaceutical preparations including prescription opiates and benzodiazepines.

The DEA has noted a significant increase in overdoses and overdose fatalities from fentanyl in the United States in recent years. A recent report \1\ from the Centers for Disease Control and Prevention (CDC) highlights this trend. According to this report, of the 41,430 drug overdose deaths occurring in the United States in 2011, 1,662 (4.0 percent) involved fentanyl.\2\ Of the 63,632 drug overdose deaths in 2016, 18,335 (28.8 percent) involved fentanyl. This was the first time that fentanyl was reported in more drug related fatalities than heroin.

\1\ Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2011-2016. National Vital Statistics Reports; vol 67 no 9. Hyattsville, MD: National Center for Health Statistics, 2018.

\2\ The fentanyl category includes fentanyl, fentanyl metabolites, precursors, and analogs.

The increase of drug overdose deaths continued into 2017. According to the CDC,\3\ there were 70,237 drug overdose deaths in the United States in 2017, an increase from the 63,632 overdose deaths recorded in 2016. Of the 70,237 overdose deaths in 2017, 47,600 (67.8 percent) involved an opioid. Deaths involving prescription opioids and heroin remained stable from 2016 to 2017; synthetic opioid overdose deaths (other than methadone), which include deaths related to fentanyl, increased 45.2 percent from 19,413 deaths in 2016 to 28,466 deaths in 2017.

\3\ Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G. Drug and Opioid-Involved Overdose Deaths--United States, 2013-2017. MMWR Morb Mortal Wkly Rep 2019;67:1419-1427.

The increase in overdose fatalities involving fentanyl coincides with a dramatic increase of law enforcement encounters of fentanyl. According to the National Forensic Laboratory Information System (NFLIS),\4\ submissions to forensic laboratories that contained fentanyl increased exponentially beginning in 2012: 694 in 2012, 1,044 in 2013, 5,537 in 2014, 15,455 in 2015, 37,294 in 2016, 61,382 in 2017, and 70,453 in 2018.

\4\ The National Forensic Laboratory Information System (NFLIS) is a national forensic laboratory reporting system that systematically collects results from drug chemistry analyses conducted by Federal, State and local forensic laboratories in the United States. NFLIS data was queried on March 26, 2019.

Role of Norfentanyl in the Synthesis of Fentanyl

Fentanyl is not a naturally occurring substance. As such, the manufacture of fentanyl requires it to be produced through synthetic organic chemistry. Synthetic organic chemistry is the process for creating a new organic molecule through a series of chemical reactions, which involve precursor chemicals. In the early 2000's, a synthetic process, commonly known as the Siegfried method, was utilized to manufacture fentanyl in several domestic and foreign clandestine laboratories. 72 FR 20039. At that time, DEA had determined that two primary synthesis routes (i.e., the Janssen method and the Siegfried method) were being used to produce fentanyl clandestinely, although it believed the Janssen synthesis route to be difficult to perform and beyond the rudimentary skills of most clandestine laboratory operators. The Siegfried synthetic route involves two important intermediates, N-phenethyl-4-piperidone (NPP) and 4-anilino-N-phenethylpiperidine (ANPP).

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The DEA controlled NPP on April 23, 2007 as a list I chemical by interim rule (72 FR 20039), which was finalized on July 25, 2008. 73 FR 43355. By final rule published on June 29, 2010, ANPP was controlled as a schedule II immediate precursor to fentanyl, with an effective date of August 30, 2010. 75 FR 37295.

In 2017, the United Nations Commission on Narcotic Drugs placed NPP and ANPP in Table I of the Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988 (1988 Convention) in response to the international increase of fentanyl on the illicit drug market. As such, member states of the United Nations were required to regulate these precursor chemicals at the national level. In addition, the People's Republic of China regulated NPP and ANPP on February 1, 2018.

Recent law enforcement information indicates that illicit manufacturers of fentanyl also use other synthetic routes in response to regulations placed on NPP and ANPP. One of these other routes is the original published synthetic pathway to fentanyl, known as the Janssen method, previously thought to be beyond the skills of most clandestine laboratory operators. This synthetic route does not involve NPP or ANPP as precursors. This synthetic pathway involves the important precursors N-(1-benzylpiperidin-4-yl)-N-phenylpropionamide (benzylfentanyl) and N-phenyl-N-(piperidin-4-yl)propionamide (norfentanyl). Benzylfentanyl is converted into norfentanyl in one chemical reaction. Norfentanyl is then subjected to one simple chemical reaction to complete the synthesis of fentanyl. The DEA is not aware of any legitimate uses of benzylfentanyl or norfentanyl other than in the synthesis of fentanyl.

According to DEA forensic laboratory data, the Janssen method was confirmed as the synthetic route used in 94 percent of 85 fentanyl drug exhibits that were evaluated to determine the synthetic route. These exhibits were seized in 2018. In addition, the number of law enforcement encounters of benzylfentanyl increased in 2017 and 2018. As stated above, benzylfentanyl is a precursor chemical used to synthesize norfentanyl in the Janssen method. According to NFLIS,\5\ there was one identification of benzylfentanyl in 2016; however, benzylfentanyl was identified in 195 reports in 2017 and 237 reports in 2018. This is believed to indicate a change in the synthetic route used by some clandestine chemists to manufacture fentanyl in efforts to evade chemical regulations on NPP and ANPP. The increase in law enforcement encounters coincides with the international control that placed NPP and ANPP in Table I of the 1988 Convention in 2017.

\5\ NFLIS data was queried on March 26, 2019.

The DEA determined that norfentanyl is commercially available from both domestic and foreign chemical suppliers. The DEA has identified 30 domestic suppliers and 22 foreign suppliers of norfentanyl from Canada (3), China (7), Germany (2), Hong Kong (1), India (1), Japan (2), Switzerland (1), and the United Kingdom (5). Of the 30 domestic suppliers of norfentanyl, only one is a DEA registrant. As it appears that these other 29 suppliers are not registered to manufacture schedule II controlled substances, it is not likely these suppliers are manufacturing fentanyl. Norfentanyl is attractive to illicit manufacturers because of the lack of chemical regulations on this substance, it is readily available from chemical suppliers, and it can easily be converted to the schedule II controlled substance fentanyl, in a one-step chemical reaction.

Designation as an Immediate Precursor

Under 21 U.S.C. 811(e), the Attorney General may place an immediate precursor into the same schedule as the controlled substance that the immediate precursor is used to make. The substance must meet the requirements of an immediate precursor under **21 U.S.C. 802**(23). The term "immediate precursor" is defined in 21 U.S.C. 802(23) meaning a substance being the principal compound used, or which is produced primarily for use in the manufacture of a controlled substance; which is an immediate chemical intermediary used or likely to be used in the manufacture of the controlled substance; and the control of which is necessary to prevent or limit the manufacture of such controlled substance.

The DEA finds that norfentanyl meets the three criteria for the definition of an immediate precursor under **21 U.S.C. 802**(23). First, DEA finds that norfentanyl is produced primarily for use in the manufacture of the schedule II controlled substance fentanyl. As stated in the preceding section, under the Janssen method, norfentanyl is typically produced from the starting material benzylfentanyl and is then subjected to a simple one-step chemical reaction to obtain the schedule II controlled substance, fentanyl. The DEA is not aware of any legitimate use of benzylfentanyl other than in the synthesis of norfentanyl, and subsequently, fentanyl. The DEA has also not identified an industrial or other use for norfentanyl beyond the manufacture of fentanyl. DEA has not identified any other legitimate uses of norfentanyl and DEA did not receive comment to the contrary during the notice and comment period of the NPRM published on September 17, 2019. 84 FR 48815.

Second, DEA finds that norfentanyl is an immediate chemical intermediary used in the manufacture of the controlled substance fentanyl. As stated earlier, norfentanyl is produced as an intermediary in the fentanyl synthetic pathway. After it is synthesized, norfentanyl is subjected to a simple chemical reaction that converts it directly to fentanyl.

Third, DEA finds that controlling norfentanyl is necessary to prevent, curtail, and limit the unlawful manufacture of the controlled substance, fentanyl. The DEA believes this action is necessary to assist in preventing the possible theft of norfentanyl from legitimate firms. The DEA believes that clandestine manufacturers will attempt to procure unregulated chemicals in their efforts to synthesize fentanyl. As a schedule II substance, norfentanyl will be safeguarded to the same degree that pharmaceutical firms now safeguard the fentanyl that they produce. Since norfentanyl is an immediate chemical intermediary in the manufacture of fentanyl, the increased level of security is necessary to prevent diversion of norfentanyl from legitimate firms. DEA also believes control is necessary to prevent unscrupulous chemists from synthesizing norfentanyl and selling it (as an unregulated material) through the internet and other channels to individuals who may wish to acquire an unregulated precursor for the purpose of manufacturing fentanyl, a schedule II controlled substance.

The DEA believes that the control of norfentanyl is necessary to prevent its production and use in the illicit manufacture of fentanyl. Therefore, DEA is designating norfentanyl as an immediate precursor of fentanyl, a schedule II controlled substance, pursuant to **21 U.S.C. 802**(23) and 21 U.S.C. 811(e).

Placement in Schedule II--Findings Required Under CSA Immediate Precursor Provisions

Pursuant to 21 U.S.C. 811(e), once norfentanyl is designated as an immediate precursor under **21 U.S.C. 802**(23), it may be placed directly into schedule II (or a schedule with a higher numerical designation). The immediate precursor provision in 21 U.S.C. 811(e)

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permits DEA to schedule an immediate precursor "without regard to the findings required by" **section 811(a) or section 812(b)** and "without regard to the procedures" prescribed by section 811(a) and (b). Accordingly, DEA need not address the "factors determinative of control" in section 811 or the findings required for placement in schedule II in section 812(b)(2). Based on the finding that norfentanyl is an "immediate precursor" for fentanyl, DEA is hereby placing norfentanyl directly into schedule II.

NPRM Comments

As part of the proposed rulemaking published on September 17, 2019 (84 FR 48815), DEA specifically solicited input from all potentially affected parties regarding: (1) The types of legitimate industries using norfentanyl; (2) the legitimate uses of norfentanyl; (3) the size of the domestic market for norfentanyl; (4) the number of manufacturers of norfentanyl; (5) the number of distributors of norfentanyl; (6) the level of import and export of norfentanyl; (7) the potential burden these proposed regulatory controls of norfentanyl may have on legitimate commercial activities; (8) the potential number of individuals/firms that may be adversely affected by these proposed regulatory controls (particularly with respect to the impact on small businesses); and (9) any other information on the manner of manufacturing, distribution, consumption, storage, disposal, and uses of norfentanyl by industry and others.

As part of the proposed rulemaking published on September 17, 2019 (84 FR 48815), DEA solicited information on any possible legitimate uses of norfentanyl unrelated to fentanyl production (including industrial uses) in order to assess the potential commercial impact of scheduling norfentanyl. The DEA searched information in the public domain for legitimate uses of norfentanyl and could not document legitimate commercial uses for norfentanyl other than as an intermediary chemical in the manufacture of fentanyl. DEA sought, however, to document any unpublicized use(s) and other proprietary use(s) of norfentanyl not in the public domain. Therefore, DEA solicited comment on the uses of norfentanyl in the legitimate marketplace. The DEA also solicited comment on the regulatory burden to legitimate commercial activities that would result from the placement of norfentanyl in schedule II of the CSA. The DEA did not receive comment on these topics.

The DEA invited all interested parties to provide any information on any legitimate uses of norfentanyl in industry, commerce, academia, research and development, or other applications. The DEA sought both quantitative and qualitative data; however, DEA did not receive comments on these topics.

The DEA received 15 comments in response to the NPRM. Thirteen of the 15 commenters were in support of controlling norfentanyl as a schedule II immediate precursor. The other two commenters did not specifically object to this rule. One of those two commenters stated that substance abuse is a public health issue and not a law enforcement issue. The other stated that this rule is not sufficient to disrupt the fentanyl market in the United States because illicit fentanyl is not produced in the United States. The commenter proposed access restriction and harm reduction strategies, including increased public awareness of drugs mixed with fentanyl and increased law enforcement at entry locations, as additional recommendations to reduce fentanyl misuse and abuse in the United States.

Of the 13 commenters in support of controlling norfentanyl as a schedule II immediate precursor, four commenters also included statements that the control of norfentanyl is not the only solution to address the opioid epidemic. These commenters stated that control of norfentanyl will not solve the issue of fentanyl being shipped into our country from foreign producers; that control of norfentanyl is not the only policy that should be addressed and implemented, and that alternate pathways to fentanyl should be monitored; and that control of norfentanyl will not end the opioid epidemic.

DEA response: The DEA appreciates the comments in support of controlling norfentanyl as a schedule II immediate precursor. The DEA is concerned with the abuse of illicitly manufactured fentanyl in the United States and abroad. While DEA remains aware that a comprehensive approach, to include community outreach and education, is required to combat the opioid epidemic, DEA believes that supply reduction strategies, which this rule attempts to address, are important aspects to reduce drug abuse in the United States. The control of norfentanyl as a schedule II immediate precursor is one aspect of the overall effort to combat the opioid epidemic. The DEA believes this rule will have a significant effect on reducing the supply of illicitly manufactured fentanyl.

With respect to the comments about illicit fentanyl being manufactured outside of the United States and shipped into the country from foreign producers, the designation of norfentanyl as a schedule II immediate precursor will subject this substance to the regulatory requirements of schedule II substances, including the import and export regulations. **21 CFR part 1312.** The DEA believes that regulating the import and export of norfentanyl will reduce the quantity of norfentanyl destined to illicit fentanyl manufacturers, both domestically and internationally, by removing the United States as a transshipment point and as a source of diverted norfentanyl to foreign illicit fentanyl manufacturers.

The DEA is the leading agency on enforcement of drug control laws and remains committed to protecting the public by interrupting and reducing drug supply and availability in the United States. The DEA believes that the control of norfentanyl as an immediate precursor of the schedule II controlled substance fentanyl will have a significant impact on reducing the supply of illicitly manufactured fentanyl; however, DEA remains aware that supply reduction is not the only aspect of combatting the opioid epidemic. The DEA realizes that a comprehensive approach, to include community outreach and education, is required to combat the opioid epidemic. In response to the comment regarding access restriction and harm reduction strategies and the comment stating that substance abuse is a public health issue and not a law enforcement issue, DEA intends this scheduling action to reduce the supply of illicitly manufactured fentanyl, which is part of a multi-faceted strategy to combat the opioid epidemic. DEA continues to work with other federal agencies on holistic and comprehensive approaches to reduce drug abuse; however, such approaches are beyond the scope of this rule.

Requirements for Handling Norfentanyl

This rulemaking finalizes two actions. It (1) designates norfentanyl as an immediate precursor for the schedule II controlled substance, fentanyl, under the definition set forth in **21 U.S.C. 802**(23); and (2) controls norfentanyl as a schedule II substance pursuant to the authority in **21 U.S.C. 811**(e).

The scheduling of norfentanyl as an immediate precursor of the schedule II controlled substance, fentanyl, subjects norfentanyl to all of the regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, dispensing, importing, and exporting of a schedule II controlled substance. The regulatory requirements will include the following:

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1. *Registration.* Any person who manufactures, distributes, dispenses, imports, or exports norfentanyl, engages in research with respect to norfentanyl, or proposes to engage in such activities will be required to submit an application and be accepted for schedule II registration in accordance with **21 CFR part 1301.**

2. *Security.* Norfentanyl will be subject to schedule II security requirements. In order to prevent diversion, norfentanyl will be manufactured, distributed, and stored in accordance with the standards for physical security and the operating procedures set forth in **21 CFR 1301.71, 1301.72**(a), (c), and (d), **1301.73, 1301.74, 1301.75**(b),(c), and (d) **1301.76,** and **1301.77.**

3. *Labeling and Packaging.* All labels and labeling for commercial containers of norfentanyl that are distributed will be required to comply with the requirements of **21 CFR 1302.03-1302.07.**

4. *Quotas.* Quotas for norfentanyl will be established pursuant to **21 CFR part 1303.**

5. *Inventory.* Every registrant who possesses any quantity of norfentanyl will be required to keep an inventory of all stocks of the substance on hand pursuant to **21 CFR 1304.03, 1304.04** and **1304.11.**

6. *Records and Reports.* Every DEA registrant will be required to maintain records and submit reports with respect to norfentanyl pursuant to **21 U.S.C. 827** and in accordance with **21 CFR parts 1304** and **1312.**

7. *Order Forms.* Every DEA registrant who distributes norfentanyl will be required to comply with the order form requirements pursuant to **21 U.S.C. 828** and in accordance with **21 CFR part 1305.**

8. *Importation and Exportation.* All importation and exportation of norfentanyl will be required to be in compliance with **21 U.S.C. 952, 953, 957,** and **958,** and in accordance with **21 CFR part 1312.**

9. *Administrative Inspection.* Places, including factories, warehouses, or other establishments and conveyances, where registrants or other regulated persons may lawfully hold, manufacture, distribute, or otherwise dispose of a controlled substance or where records relating to those activities are maintained, are controlled premises as defined in **21 U.S.C. 880**(a) and **21 CFR 1316.02**(c). The CSA allows for administrative inspections of these controlled premises as provided in **21 CFR part 1316,** subpart A. 21 U.S.C. 880.

10. *Liability.* Any activity with norfentanyl in violation of or not authorized under the Controlled Substances Act or the Controlled Substances Import and Export Act will be unlawful and potentially subject to criminal penalties. **21 U.S.C. 841-863** and **959-964.**

Regulatory Analyses

Executive Orders 12866, 13563, and 13771, Regulatory Planning and Review, Improving Regulation and Regulatory Review, and Reducing Regulation and Controlling Regulatory Costs

This rulemaking was developed in accordance with the principles of Executive Orders 12866, 13563, and 13771. Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, if regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health, and safety effects; distributive impacts; and equity). Executive Order 13563 is supplemental to and reaffirms the principles, structures, and definitions governing regulatory review as established in Executive Order 12866. Executive Order 12866 classifies a "significant regulatory action," requiring review by the Office of Management and Budget (OMB), as any regulatory action that is likely to result in a rule that may: (1) Have an annual effect on the economy of $100 million or more or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, or tribal governments or communities; (2) create a serious inconsistency or otherwise interfere with an action taken or planned by another agency; (3) materially alter the budgetary impact of entitlements, grants, user fees, or loan programs or the rights and obligations of recipients thereof; or (4) raise novel legal or policy issues arising out of legal mandates, the President's priorities, or the principles set forth in the Executive Order. DEA has determined that this rule is not a "significant regulatory action" under Executive Order 12866, section 3(f). Executive Order 13771 requires an agency, unless prohibited by law, to identify at least two existing regulations to be repealed when the agency publicly proposes for notice and comment or otherwise promulgates a new regulation.\6\ In furtherance of this requirement, Executive Order 13771 requires that the new incremental costs associated with new regulations, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations.\7\ According to guidance provided by OMB, the requirements of Executive Order 13771 only apply to each new "significant regulatory action that . . . imposes costs." \8\ This rule is not expected to be an Executive Order 13771 regulatory action because this rule is not significant under Executive Order 12866.

\6\ Sec. 2(a).

\7\ Sec. 2(c).

\8\ OMB Guidance Implementing Executive Order 13771 titled "Reducing Regulation and Controlling Regulatory Costs" (April 5, 2017).

The scheduling of norfentanyl as an immediate precursor of the schedule II controlled substance, fentanyl, subjects norfentanyl to all of the regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, dispensing, importing, and exporting of a schedule II controlled substance. Norfentanyl is the immediate chemical intermediary in a synthesis process currently used by clandestine laboratory operators for the manufacture of the schedule II controlled substance fentanyl. The distribution of illicitly manufactured fentanyl has caused an unprecedented outbreak of thousands of fentanyl-related overdoses in the United States in recent years.

The DEA has not identified any industrial use for norfentanyl, other than its role as an intermediary chemical in the manufacture of fentanyl. Based on the review of import and quota information for ANPP and fentanyl, DEA believes the vast majority, if not all, of legitimate pharmaceutical fentanyl is produced from ANPP (schedule II immediate precursor for fentanyl), not norfentanyl. The quantities of ANPP permitted in the U.S., imported or manufactured pursuant to a quota, generally correspond with the quantities of legitimate pharmaceutical fentanyl produced in the United States. Additionally, DEA is not aware of norfentanyl being used for the manufacturing of legitimate pharmaceutical fentanyl; however, DEA cannot rule out the possibility that minimal quantities of norfentanyl are used for this purpose. If there are any quantities of norfentanyl used for the manufacturing of legitimate pharmaceutical fentanyl, the quantities are believed to be small and economically insignificant.

The DEA evaluated the costs and benefits of this action.

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Costs

The DEA believes the market for norfentanyl for the legitimate manufacturing of pharmaceutical fentanyl is minimal. As stated above, the only use for norfentanyl of which DEA is aware is for the manufacturing of fentanyl. Any manufacturer, distributor, importer, or exporter of norfentanyl for the production of legitimate pharmaceutical fentanyl, if they exist at all, would incur costs. The primary costs associated with this rule include costs associated with complying with registration, physical security, labeling and packaging, quota, inventory, recordkeeping and reporting, and importation and exportation requirements. Other than the annual registration fees ($3,047 for manufacturers and $1,523 for distributors, importers, and exporters), due to the many unknowns and variability between entities, it is highly difficult to quantify the potential total cost burden of this regulation. However, any manufacturer that uses norfentanyl for legitimate pharmaceutical fentanyl production would already be registered with DEA and have all security and other handling processes in place, resulting in minimal cost. Any lost sales or profit attributed to those manufacturers or suppliers that are not for legitimate pharmaceutical fentanyl are excluded from the analysis as they are, whether passively or actively, facilitating the manufacture of illicit fentanyl.

The DEA has identified 30 domestic suppliers of norfentanyl, 29 of which are not registered with DEA to handle schedule II controlled substances. It is difficult to estimate how much norfentanyl is distributed by these suppliers. It is common for chemical distributors to have items on their catalog while not actually having any material level of sales. Based on the review of import and quota information for fentanyl and ANPP, where the quantities of ANPP imported and manufactured generally correspond with the quantities of fentanyl produced, DEA believes any quantity of sales from these distributors for the legitimate pharmaceutical fentanyl manufacturing is minimal. Suppliers for the legitimate use of norfentanyl are expected to choose the least-cost option, and stop selling the minimal quantities, if any, of norfentanyl, rather than incur the costs of complying with the regulatory requirements. Because DEA believes the quantities of norfentanyl supplied for the legitimate manufacturing of pharmaceutical fentanyl is minimal, DEA estimates that the cost of foregone sales is minimal; and thus, the cost of this rule is minimal.

This analysis excludes consideration of economic impact to those businesses that facilitate the manufacturing and distribution of norfentanyl for the manufacture of illicit fentanyl. The only use for norfentanyl of which DEA is currently aware is the manufacture of fentanyl. Although these suppliers are selling a currently unregulated substance, they wittingly or unwittingly facilitate the manufacturing of illicit fentanyl. As a law enforcement organization and as a matter of principle, DEA believes considering the economic utility of facilitating the manufacture of illicit fentanyl would be improper.

Benefits

Controlling norfentanyl is expected to prevent, curtail, and limit the unlawful manufacture and distribution of the controlled substance, fentanyl. This action is also expected to assist preventing the possible theft or diversion of norfentanyl from any legitimate firms. As a schedule II substance, norfentanyl will be safeguarded to the same degree that pharmaceutical firms now safeguard the fentanyl that they produce. The DEA also believes control is necessary to prevent unscrupulous chemists from synthesizing norfentanyl and selling it (as an unregulated material) through the internet and other channels, to individuals who may wish to acquire an unregulated precursor for the purpose of manufacturing illicit fentanyl.

In summary, DEA conducted a qualitative analysis of costs and benefits. DEA believes this action will minimize the diversion of norfentanyl. The DEA believes the market for norfentanyl for the legitimate manufacturing of pharmaceutical fentanyl is minimal. Therefore, any potential cost as a result of this regulation is minimal. Therefore, the estimated economic impact of this rule is less than $100 million in any given year.

Executive Order 12988, Civil Justice Reform

This regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of Executive Order 12988 Civil Justice Reform to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132, Federalism

This rulemaking does not have federalism implications warranting the application of Executive Order 13132. The rule does not have substantial direct effects on the States, on the relationship between the national government and the States, or the distribution of power and responsibilities among the various levels of government.

Executive Order 13175, Consultation and Coordination With Indian Tribal Governments

This rule does not have tribal implications warranting the application of Executive Order 13175. This rule does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal Government and Indian tribes, or on the distribution of power and responsibilities between the Federal Government and Indian tribes.

Regulatory Flexibility Act

The Acting Administrator, in accordance with the Regulatory Flexibility Act (5 U.S.C. 601-612) (RFA), has reviewed this rule and by approving it certifies that it will not have a significant economic impact on a substantial number of small entities. As discussed above, the scheduling of norfentanyl as an immediate precursor of the schedule II controlled substance, fentanyl, subjects norfentanyl to all of the regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, dispensing, importing, and exporting of a schedule II controlled substance. Norfentanyl is the immediate chemical intermediary in a synthesis process currently used by clandestine laboratory operators for the illicit manufacture of the schedule II controlled substance fentanyl. The distribution of illicitly manufactured fentanyl has caused an unprecedented outbreak of thousands of fentanyl-related overdoses in the United States in recent years.

The DEA has not identified any use for norfentanyl, other than its role as an intermediary chemical in the manufacture of fentanyl. Based on the review of import and quota information for ANPP and fentanyl, DEA believes the vast majority, if not all, of legitimate pharmaceutical fentanyl is produced from ANPP (schedule II immediate precursor for fentanyl), not norfentanyl. The quantities of ANPP permitted in the U.S., imported or manufactured pursuant to a quota, generally correspond with the quantities of

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legitimate pharmaceutical fentanyl produced in the United States. Additionally, DEA is not aware of norfentanyl being used for the manufacturing of legitimate pharmaceutical fentanyl; however, DEA cannot rule out the possibility that minimal quantities of norfentanyl are used for this purpose. If there are any quantities of norfentanyl used for the manufacturing of legitimate pharmaceutical fentanyl, the quantities are believed to be small and economically insignificant.

The DEA has identified 30 domestic suppliers of norfentanyl. Based on the Small Business Administration size standard for chemical distributors and Statistics of United States Business data, 94.5 percent or 28.4 (rounded to 28) are estimated to be small entities. It is difficult to know how much norfentanyl is distributed by these suppliers. It is common for chemical distributors to have items on their catalog while not actually having any material level of sales. Based on the review of import and quota information for fentanyl and ANPP, where the quantities of ANPP imported and manufactured generally correspond with the quantities of fentanyl produced, DEA believes any quantity of sales from these distributors for the legitimate pharmaceutical fentanyl manufacturing is minimal. Therefore, DEA estimates the cost of this rule on any affected small entity is minimal.

Because of these facts, this rule will not result in a significant economic impact on a substantial number of small entities.

Unfunded Mandates Reform Act of 1995

On the basis of information contained in the "Regulatory Flexibility Act" section above, DEA determined and certifies pursuant to the Unfunded Mandates Reform Act of 1995 (UMRA), 2 U.S.C. 1501 et seq., that this action will not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted for inflation) in any one year * * *." Therefore, neither a Small Government Agency Plan nor any other action is required under provisions of UMRA.

Paperwork Reduction Act

This action does not impose a new collection of information under the Paperwork Reduction Act, 44 U.S.C. 3501-3521. This action does not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, drug traffic control, reporting and recordkeeping requirements.

For the reasons set out above, DEA amends 21 CFR part 1308 as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

- 1. The authority citation for 21 CFR part 1308 continues to read as follows:

  Authority: 21 U.S.C. 811, 812, 871(b), 956(b), unless otherwise noted.

- 2. Amend **Sec. 1308.12** by adding paragraph (g)(3)(ii) to read as follows.

Sec. 1308.12 **Schedule II.**

* * * * *

(g) * * *

(3) * * *

(ii) *N*-phenyl-*N*-(piperidin-4-yl)propionamide (norfentanyl)	8366

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Dated: March 5, 2020.

Uttam Dhillon,
Acting Administrator.

[FR Doc. 2020-07381 Filed 4-16-20; 8:45 am]

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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-503]

Schedules of Controlled Substances: Placement of Brexanolone in Schedule IV

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final rule.

SUMMARY: This final rule adopts without change an interim final rule with request for comments published in the Federal Register on June 17, 2019. That interim final rule placed the substance brexanolone (3α-hydroxy-5α-pregnan-20-one), including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible, in schedule IV of the Controlled Substances Act. With the issuance of this final rule, the Drug Enforcement Administration maintains brexanolone in schedule IV of the Controlled Substances Act.

DATES: Effective January 24, 2020.

FOR FURTHER INFORMATION CONTACT: Scott Brinks, Diversion Control Division, Drug Enforcement

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Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (571) 362-3261.

SUPPLEMENTARY INFORMATION:

Background

On June 17, 2019, the Drug Enforcement Administration (DEA) published an interim final rule to make brexanolone (including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible) a schedule IV controlled substance. 84 FR 27938. The interim final rule provided an opportunity for interested persons to submit comments, as well as file a request for hearing or waiver of hearing, on or before July 17, 2019.

Comments Received

The DEA received three comments in response to the interim final rule to control brexanolone as a schedule IV substance of the Controlled Substances Act (CSA). Two of the three commenters were in support of the interim final rule to place brexanolone in schedule IV of the CSA, and one commenter was opposed to the placement of brexanolone in schedule IV of the CSA. The DEA did not receive any requests for hearing or waiver of hearing.

Support of the Interim Final Rule

Two commenters supported controlling brexanolone as a schedule IV controlled substance. These commenters indicated support for scheduling brexanolone under the CSA due to its similarity to other schedule IV sedatives including midazolam and alprazolam.

DEA Response. The DEA appreciates the support for this rulemaking.

Opposition to the Interim Final Rule

A commenter opposed the interim final rule to control brexanolone as a schedule IV substance. Although the commenter did not state if or where brexanolone should be scheduled, the commenter expressed concerns about brexanolone's adverse health effects such as exposure of an antidepressant to infants through breastmilk, potential for "hidden side effects," and drug-associated dizziness and somnolence affecting the maternal care of the infant.

DEA Response. The commenter's concerns about adverse health effects of brexanolone are related to the Food and Drug Administration's (FDA) approval process (such as weighing the benefits versus risks) and outside of the scope of this rulemaking. The FDA approved a new drug application (NDA) for Zulresso (brexanolone)--a substance identified as having abuse potential pursuant to **21 U.S.C. 811**(f)--and provided the DEA with a scheduling recommendation for control of brexanolone in schedule IV of the CSA. As provided in 21 U.S.C. 811(j), the scheduling recommendation by the Department of Health and Human Services (HHS) and the FDA approval of the NDA necessitated the DEA review and scheduling action. The DEA made the findings required under **21 U.S.C. 812**(b)(4) for the placement of brexanolone in schedule IV. The scheduling determination was based on a comprehensive evaluation of all available data as related to the eight-factor analysis pursuant to 21 U.S.C. 811(c), but not by a single metric such as adverse health effects as expressed by this commenter. As stated in the interim final rule, after careful consideration of data from preclinical and clinical studies, the DEA concurred with the HHS recommendation that brexanolone has abuse potential comparable to other schedule IV benzodiazepines such as midazolam and alprazolam, and therefore, supported and continues to support through the promulgation of this final rule placement of brexanolone in schedule IV under the CSA. None of the commenter's concerns about brexanolone's potential health effects undermine any aspect of the interim final rule's analysis.

Based on the rationale set forth in the interim final rule, the DEA adopts the interim final rule without change.

Requirements for Handling Brexanolone

As indicated above, brexanolone has been a schedule IV substance by virtue of the interim final rule issued by DEA in June 2019. Therefore, this final rule does not alter the regulatory requirements applicable to handlers of brexanolone that have been in place since that time. Nonetheless, for informational purposes, we restate here those requirements. Brexanolone is subject to the CSA's schedule IV regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, reverse distribution, dispensing, importing, exporting, research, and conduct of instructional activities and chemical analysis with, and possession involving schedule IV substances, including the following:

1. *Registration.* Any person who handles (manufactures, distributes, reverse distributes, dispenses, imports, exports, engages in research, or conducts instructional activities or chemical analysis with, or possesses) brexanolone, or who desires to handle brexanolone, must be registered with the DEA to conduct such activities pursuant to **21 U.S.C. 822, 823, 957,** and **958** and in accordance with **21 CFR parts 1301** and **1312.** Any person who intends to handle brexanolone and is not registered with the DEA must submit an application for registration and may not handle brexanolone, unless the DEA approves that application for registration, pursuant to 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312.

2. *Disposal of stocks.* Any person who obtains a schedule IV registration to handle brexanolone, but who subsequently does not desire or is not able to maintain such registration, must surrender all quantities of brexanolone or may transfer all quantities of brexanolone to a person registered with the DEA in accordance with **21 CFR part 1317,** in addition to all other applicable federal, state, local, and tribal laws.

3. *Security.* Brexanolone is subject to schedule III-V security requirements and must be handled and stored in accordance with **21 CFR 1301.71-1301.93.**

4. *Labeling and Packaging.* All labels, labeling, and packaging for commercial containers of brexanolone must comply with **21 U.S.C. 825** and **958(e),** and be in accordance with **21 CFR part 1302.**

5. *Inventory.* Every DEA registrant who possesses any quantity of brexanolone was required to keep an inventory of all stocks of brexanolone on hand, as of June 17, 2019, pursuant to **21 U.S.C. 827** and **958(e),** and in accordance with **21 CFR 1304.03, 1304.04,** and **1304.11.**

6. *Records and Reports.* DEA registrants must maintain records and submit reports for brexanolone, pursuant to **21 U.S.C. 827** and **958(e),** and in accordance with **21 CFR parts 1304, 1312,** and **1317.**

7. *Prescriptions.* All prescriptions for brexanolone or products containing brexanolone must comply with **21 U.S.C. 829,** and be issued in accordance with **21 CFR parts 1306** and **1311,** subpart C.

8. *Manufacturing and Distributing.* In addition to the general requirements of the CSA and DEA regulations that are applicable to manufacturers and distributors of schedule IV controlled substances, such registrants should be advised that (consistent with the foregoing considerations) any manufacturing or distribution of brexanolone may only be for the legitimate purposes consistent with the drug's labeling, or for research activities authorized by the Federal Food, Drug, and Cosmetic Act and the CSA.

9. *Importation and Exportation.* All importation and exportation of

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brexanolone must be in compliance with **21 U.S.C. 952, 953, 957,** and **958,** and in accordance with **21 CFR part 1312.**

10. *Liability.* Any activity involving brexanolone not authorized by, or in violation of, the CSA or its implementing regulations, is unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

Regulatory Analyses

Administrative Procedure Act

This final rule, without change, affirms the amendment made by the interim final rule that is already in effect. Section 553 of the Administrative Procedure Act (APA) (5 U.S.C. 553) generally requires notice and comment for rulemakings. However, **21 U.S.C. 811** provides that in cases where a new drug is (1) approved by the HHS and (2) HHS recommends control in CSA schedule II-V, the DEA shall issue an interim final rule scheduling the drug within 90 days. Additionally, the law specifies that the rulemaking shall become immediately effective as an interim final rule without requiring the DEA to demonstrate good cause. The DEA issued an interim final rule on June 17, 2019 and solicited public comments on that rule. Section 811 further states that after giving interested persons the opportunity to comment and to request a hearing, "the Attorney General shall issue a final rule in accordance with the scheduling criteria of subsections (b), (c), and (d) of this section and **section 812**(b) of" the CSA. 21 U.S.C. 811(j)(3). The DEA is now responding to the comments submitted by the public and issuing the final rule, in conformity with the APA and the procedure required by 21 U.S.C. 811.

Executive Orders 12866, 13563, and 13771, Regulatory Planning and Review, Improving Regulation and Regulatory Review, and Reducing Regulation and Controlling Regulatory Costs

In accordance with **21 U.S.C. 811**(a) and (j), this scheduling action is subject to formal rulemaking procedures performed "on the record after opportunity for a hearing," which are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth the procedures and criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget (OMB) pursuant to section 3(d)(1) of Executive Order 12866 and the principles reaffirmed in Executive Order 13563.

This final rule is not an Executive Order 13771 regulatory action pursuant to Executive Order 12866 and OMB guidance.\1\

\1\ Office of Mgmt. & Budget, Exec. Office of The President, Interim Guidance Implementing Section 2 of the Executive Order of January 30, 2017 Titled "Reducing Regulation and Controlling Regulatory Costs" (Feb. 2, 2017).

Executive Order 12988, Civil Justice Reform

This regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of Executive Order 12988 to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132, Federalism

This final rulemaking does not have federalism implications warranting the application of Executive Order 13132. The final rule does not have substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government.

Executive Order 13175, Consultation and Coordination With Indian Tribal Governments

This final rule does not have tribal implications warranting the application of Executive Order 13175. It does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal government and Indian tribes, or on the distribution of power and responsibilities between the Federal government and Indian tribes.

Regulatory Flexibility Act

The Regulatory Flexibility Act (RFA) (5 U.S.C. 601-612) applies to rules that are subject to notice and comment under section 553(b) of the APA. Under **21 U.S.C. 811**(j), the DEA was not required to publish a general notice of proposed rulemaking prior to this final rule. Consequently, the RFA does not apply.

Unfunded Mandates Reform Act of 1995

In accordance with the Unfunded Mandates Reform Act (UMRA) of 1995, 2 U.S.C. 1501 et seq., the DEA has determined that this action would not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted for inflation) in any one year." Therefore, neither a Small Government Agency Plan nor any other action is required under UMRA of 1995.

Paperwork Reduction Act of 1995

This action does not impose a new collection of information requirement under the Paperwork Reduction Act of 1995. 44 U.S.C. 3501-3521. This action would not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Congressional Review Act

This final rule is not a major rule as defined by the Congressional Review Act (CRA), 5 U.S.C. 804. This rule will not result in: An annual effect on the economy of $100,000,000 or more; a major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; or significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of U.S.-based companies to compete with foreign based companies in domestic and export markets. However, pursuant to the CRA, the DEA is submitting a copy of this final rule to both Houses of Congress and to the Comptroller General.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

Accordingly, the interim final rule amending 21 CFR part 1308, which published on June 17, 2019 (**84 FR 27938**), is adopted as a final rule without change.

Dated: January 3, 2020.

Uttam Dhillon,
Acting Administrator.

[FR Doc. 2020-00669 Filed 1-23-20; 8:45 am]

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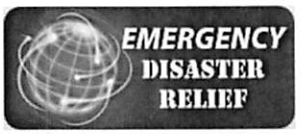

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DIVERSION CONTROL DIVISION

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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-600]

Schedules of Controlled Substances: Placement of Lemborexant in Schedule IV

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Interim final rule with request for comments.

SUMMARY: On December 20, 2019, the U.S. Food and Drug Administration approved a new drug application for Dayvigo (lemborexant) tablets for oral use. Lemborexant is chemically known as (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropane-1-carboxamide. The Department of Health and Human Services provided the Drug Enforcement Administration (DEA) with a scheduling recommendation to place lemborexant in schedule IV of the Controlled Substances Act (CSA). In accordance with the CSA, as amended by the Improving Regulatory Transparency for New Medical Therapies Act, DEA is hereby issuing an interim final rule placing lemborexant, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible, in schedule IV of the CSA.

DATES: The effective date of this rulemaking is April 7, 2020. Interested persons may file written comments on this rulemaking in accordance with **21 U.S.C. 811**(j)(3) and **21 CFR 1308.43**(g). Electronic comments must be submitted, and written comments must be postmarked, on or before May 7, 2020. Commenters should be aware that the electronic Federal Docket Management System will not accept comments after 11:59 p.m. Eastern Time on the last day of the comment period.

Interested persons may file a request for hearing or waiver of hearing in accordance with

21 U.S.C. 811(j)(3) and **21 CFR 1308.44**. Requests for hearing and waivers of an opportunity for a hearing or to participate in a hearing, together with a written statement of position on the matters of fact and law asserted in the hearing, must be received on or before May 7, 2020.

ADDRESSES: To ensure proper handling of comments, please reference "Docket No. DEA-600" on all correspondence, including any attachments.

- *Electronic comments:* The Drug Enforcement Administration (DEA) encourages that all comments be submitted electronically through the Federal eRulemaking Portal, which provides the ability to type short comments directly into the comment field on the web page or attach a file for lengthier comments. Please go to http://www.regulations.gov and follow the online instructions at the site for submitting comments. Upon completion of your submission, you will receive a Comment Tracking Number for your comment. Please be aware that submitted comments are not instantaneously available for public view on Regulations.gov. If you have received a Comment Tracking Number, your comment has been successfully submitted and there is no need to resubmit the same comment.
- *Paper comments:* Paper comments that duplicate the electronic submission are not necessary and are discouraged. Should you wish to mail a paper comment in lieu of an electronic comment, it should be sent via regular or express mail to: Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrissette Drive, Springfield, VA 22152.
- *Hearing requests:* All requests for hearing and waivers of participation, together with a written statement regarding his position on the matter of fact and law involved in such hearing, must be sent to: Drug Enforcement Administration. Attn: Administrator, 8701 Morrissette Drive, Springfield, Virginia 22152. All requests for hearing and waivers of participation should also be sent to: (1) Drug Enforcement Administration, Attn: Hearing Clerk/LJ. 8701 Morrissette Drive, Springfield, Virginia 22152: and (2) Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW. 8701 Morrissette Drive, Springfield, Virginia 22152.

FOR FURTHER INFORMATION CONTACT: Scott A. Brinks, Regulatory Drafting and Policy Support Section, Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (571) 362-3261.

SUPPLEMENTARY INFORMATION:

Posting of Public Comments

Please note that all comments received are considered part of the public record. They will, unless reasonable cause is given, be made available by the Drug Enforcement Administration (DEA) for public inspection online at http://www.regulations.gov. Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter. The Freedom of Information Act applies to all comments received. If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want it to be made publicly available, you must include the phrase "PERSONAL IDENTIFYING INFORMATION" in the first paragraph of your comment. You must also place all of the personal identifying information you do not want made publicly available in the first paragraph of your comment and identify what information you want redacted. If you want to submit confidential business information as part of your comment, but do not want it to be made publicly available, you must include the phrase "CONFIDENTIAL BUSINESS INFORMATION" in the first paragraph of your comment. You must also prominently identify the confidential business information to be redacted within the comment.

Comments containing personal identifying information and confidential business information identified as directed above will generally be made publicly available in redacted form. If a comment has so much confidential business information or personal identifying information that it cannot be effectively redacted, all or part of that comment may not be made publicly available. Comments posted to http://www.regulations.gov may include any personal identifying information (such as name, address, and phone number) included in the text of your electronic submission that is not identified as directed above as confidential.

An electronic copy of this document and supplemental information, including the complete Department of Health and Human Services (HHS) and DEA eight-factor analyses, to this interim final rule are available at http://www.regulations.gov for easy reference.

Request for Hearing or Appearance; Waiver

Pursuant to **21 U.S.C. 811**(a), this action is a formal rulemaking "on the record after opportunity for a hearing." Such proceedings are conducted pursuant to the provisions of the Administrative Procedure Act (APA), 5 U.S.C. 551-559. **21 CFR 1308.41-1308.45; 21 CFR part 1316**, subpart D. Interested persons may file

requests for a hearing or notices of intent to participate in a hearing in conformity with the requirements of **21 CFR 1308.44**(a) or (b), and include a statement of interest in the proceeding and the objections or issues, if any,

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concerning which the person desires to be heard. **21 CFR 1316.47**(a). Any interested person may file a waiver of an opportunity for a hearing or to participate in a hearing together with a written statement regarding the interested person's position on the matters of fact and law involved in any hearing as set forth in **21 CFR 1308.44**(c).

All requests for a hearing and waivers of participation together with a written statement of position on the matters of fact and law involved in such hearing, must be sent to DEA using the address information provided above.

Background and Legal Authority

Under the Improving Regulatory Transparency for New Medical Therapies Act, Public Law 114-89, 2(b), 129 tat. 700 (2015), DEA is required to commence an expedited scheduling action with respect to certain new drugs approved by the Food and Drug Administration (FDA). As provided in **21 U.S.C. 811**(j), this expedited scheduling is required where both of the following conditions apply: (1) The Secretary of HHS has advised DEA that a New Drug Application (NDA) has been submitted for a drug that has a stimulant, depressant, or hallucinogenic effect on the central nervous system (CNS), and that it appears that such drug has an abuse potential; and (2) the Secretary of HHS recommends that DEA control the drug in schedule II, III, IV, or V pursuant to 21 U.S.C. 811(a) and (b). In these circumstances. DEA is required to issue an interim final rule controlling the drug within 90 days.

The law further states that the 90-day timeframe starts the later of: (1) The date DEA receives HHS' scientific and medical evaluation and scheduling recommendation, or (2) the date DEA receives notice of the NDA approval by HHS. In addition, the law specifies that the rulemaking shall become immediately effective as an interim final rule without requiring DEA to demonstrate good cause therefore. Thus, the purpose of subsection (j) is to speed the process by which DEA schedules newly approved drugs that are currently either in schedule I or not controlled (but which have sufficient abuse potential to warrant control) so that such drugs may be marketed without undue delay following FDA approval.\1\

\1\ Given the parameter of subsection (j), in DEA's view, it would not apply to a reformulation of a drug containing a substance currently in schedules II through V for which an NDA has recently been approved.

Subsection (j) further provides that the interim final rule shall give interested persons the opportunity to comment and to request a hearing. After the conclusion of such proceedings, DEA must issue a final rule in accordance with the scheduling criteria of subsections **21 U.S.C. 811**(b), (c), and (d) and **21 U.S.C. 812**(b).

Lemborexant [(1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropane-1-carboxamide] is a new molecular entity with CNS depressant properties. Lemborexant acts as an antagonist at both orexin-1 and orexin-2 receptors (OX1R and OX2R, respectively). On December 27, 2018, Eisai, Inc., submitted an NDA for Dayvigo (lemborexant), 5 and 10 mg oral tablets, with the proposed dosage suggestion of 5 mg, not to exceed a maximum dose of 10 mg once a day. On March 9, 2020, DEA received a letter from FDA, dated March 5, 2020, notifying DEA that FDA, on December 20, 2019, approved the NDA for Dayvigo (lemborexant), under section 505(c) of the Federal Food, Drug, and Cosmetic Act (FDCA), for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.\2\ Lemborexant has not been marketed in any other country for any medical indication.

\2\ https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/212028Orig1s000ltr.pdf, accessed March 11, 2020.

Determination To Schedule Lemborexant

On January 9, 2020, DEA received from HHS a scientific and medical evaluation (dated December 19, 2019) entitled "Basis for the Recommendation to Control Lemborexant and its Salts in Schedule IV of the Controlled Substances Act" and a scheduling recommendation. Pursuant to **21 U.S.C. 811**(b) and (c), this document contained an eight-factor analysis of the abuse potential, legitimate medical use, and dependence liability of lemborexant, along with HHS's recommendation to control lemborexant and its salts under schedule IV of the CSA.

In response, DEA reviewed the scientific and medical evaluation and scheduling recommendation provided by HHS, along with all other relevant data, and completed its own eight-factor review pursuant to **21 U.S.C. 811**(c). DEA concluded that lemborexant meets the **21 U.S.C. 812**(b)(4) criteria for placement in schedule IV of the CSA.

Pursuant to **subsection 811**(j), and based on HHS's recommendation, the NDA approval by HHS/FDA, and DEA's determination, DEA is issuing this interim final rule to schedule lemborexant as a schedule IV controlled substance under the CSA.

Included below is a brief summary of each factor as analyzed by HHS and DEA, and as considered by DEA in its scheduling action. Please note that both DEA and HHS analyses are available in their entirety under "Supporting Documents" in the public docket for this interim final rule at http://www.regulations.gov, under Docket Number "DEA-600." Full analysis of, and citations to, the information referenced in the summary may also be found in the supporting and related material.

1. Its Actual or Relative Potential for Abuse

As noted by HHS, lemborexant is a new molecular entity that has not been marketed in the United States or any other country. Thus, evidence regarding its diversion, illicit manufacture, or deliberate ingestion is currently lacking. DEA notes that there are no reports for lemborexant in the National Forensic Laboratory Information System (NFLIS),\3\ which collects drug identification results from drug cases submitted to and analyzed by state and local forensic laboratories. There were also no reports in STARLIMS,\4\ DEA's laboratory drug evidence data system of record.

\3\ NFLIS represents an important resource in monitoring illicit drug trafficking, including the diversion of legally manufactured pharmaceuticals into illegal markets. NFLIS is a comprehensive information system that includes data from forensic laboratories that handle more than 96% of an estimated 1.0 million distinct annual State and local drug analysis cases. NFLIS includes drug chemistry results from completed analyses only. While NFLIS data is not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. See 76 FR 77330, 77332, Dec. 12, 2011. NFLIS data were queried January 15, 2020.

\4\ On October 1, 2014, DEA implemented STARLIMS (a web-based, commercial laboratory information management system) to replace the System to Retrieve Information from Drug Evidence (STRIDE) as its laboratory drug evidence data system of record. DEA laboratory data submitted after September 30, 2014, are reposited in STARLIMS. STARLIMS data were queried January 15, 2020.

As stated by HHS, lemborexant is a sedative that is highly selective for both the OX1R and OX2R receptors and has little to no affinity to other CNS receptor sites associated with abuse potential. In a clinical study investigating the abuse potential of lemborexant, HHS concluded that lemborexant produced subjective responses that were similar to those for the schedule IV sedative suvorexant.

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2. Scientific Evidence of Its Pharmacological Effects, if Known

According to HHS, lemborexant primarily acts as a dual orexin receptor antagonist and does not bind with any other CNS receptors that are typically associated with abuse, such as opioid or cannabinoid receptors, GABAergic, and other ion channels. According to HHS, general behavioral studies in animals indicate that acute oral administration of lemborexant using supratherapeutic doses (100, 300, and 1000 mg/kg), produced no overt behavioral changes in hindlimb foot splay, forelimb grip strength, hindlimb grip strength, and rectal temperature in cage-side, hand-held, and open-field using functional observational methods. Additionally, lemborexant, even at supratherapeutic doses, does not significantly impair motor coordination. In drug discrimination studies, which are used to predict subjective effects in humans, lemborexant and suvorexant (a schedule IV substance which is another known dual orexin receptor antagonist) did not fully mimic stimulus effects of zolpidem, a schedule IV sedative. In a self-administration study in rhesus monkeys, the rewarding effects of lemborexant were insufficient to produce reinforcement.

According to HHS, in a human abuse potential (HAP) study conducted by the Sponsor, lemborexant (at therapeutic and supratherapeutic doses) produced statistically significant increases on positive subjective measures in the bipolar visual analog scale (VAS) (i.e., Drug Liking, Overall Drug Liking, Good Effects, High, Stoned, and Take Drug Again) that were greater than placebo and statistically similar to suvorexant and/or zolpidem (schedule IV substances). With respect to two subjective measures, such as drowsiness and sedation, lemborexant, similar to zolpidem and suvorexant, produced statistically significantly greater scores than placebo. HHS concluded that lemborexant produces positive subjective effects and has an abuse potential similar to that of schedule IV sedatives, such as suvorexant and zolpidem, which were used as positive controls in the aforementioned study. According to HHS, in multiple-dose Phase I studies, lemborexant produced dose-dependent "abnormal dreams." There were few incidents of abuse-related adverse events (AEs), such as "euphoric mood," "disturbance in attention," and "memory impairment." Furthermore, in Phase 2 clinical studies, lemborexant produced dose dependent somnolence. This response was considered appropriate given the proposed therapeutic use for lemborexant as a treatment for insomnia. No additional abuse-related AEs were reported by participants at an incidence greater than 1.0 percent. As per the adverse event data obtained from Phase 1 and Phase \2/3\ clinical safety and efficacy trials, there were no significant abuse-related signals.

3. The State of Current Scientific Knowledge Regarding the Drug or Other Substance

Lemborexant is a new molecular entity, chemically known as (1R,2S)-2-[(2,4-dimethylpyrimidin-5-yl)oxymethyl]-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropane-1-carboxamide. It is nearly insoluble in water and heptane; "sparingly" soluble in 1-octanol; very soluble in dimethyl sulfoxide; and freely soluble in methanol, acetone, ethyl acetate, and benzyl alcohol. Additionally, lemborexant is soluble in acetonitrile and ethanol. On December 20, 2019, FDA approved an NDA for lemborexant for medical use for the treatment of insomnia in adult patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance. Thus, lemborexant has an accepted medical use in the United States. Lemborexant will be marketed as a once daily tablet taken before bedtime, with at least 7 hours remaining before the planned time of awakening. The recommended dose for lemborexant is 5 mg; however, the dosage may be increased to 10 mg based on clinical response and tolerability.\5\

\5\ https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212028s000lbl.pdf, accessed February 6, 2020.

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4. Its History and Current Pattern of Abuse

There is no information available relating to the history and current pattern of abuse of lemborexant because this drug is not currently marketed in any country. As stated in Factor 1, DEA notes that there has been no diversion of lemborexant based on NFLIS and STARLIMS data. HHS notes that lemborexant produces abuse-related signals and abuse potential similar to that of the schedule IV controlled substance suvorexant.

5. The Scope, Duration, and Significance of Abuse

Lemborexant as a single active ingredient in a drug product is currently not marketed in any country. Thus, information on the scope, duration, and significance of abuse for lemborexant is lacking. As described in Factor 4, NFLIS and STARLIMS databases have no evidence of law enforcement encounters of lemborexant. However, as HHS notes, data from preclinical and clinical studies summarized in Factor 2 indicate that the scope, duration, and significance of abuse for lemborexant would be similar to those of suvorexant, a schedule IV substance. As stated by HHS, data from animal and human studies indicate that lemborexant has an abuse potential similar to that of suvorexant.

6. What, if Any, Risk There Is to the Public Health

As stated by HHS, the public health risk associated with lemborexant is largely a risk to the individual due to its abuse potential. The extent of abuse potential of a drug is an indication of its public health risk. Data from the preclinical and clinical studies suggest that the abuse potential of lemborexant is similar to schedule IV substances, such as suvorexant and zolpidem. Lemborexant, similar to schedule IV sedatives, is likely to pose a public health risk of abuse upon marketing in the United States.

7. Its Psychic or Physiological Dependence Liability

Physical dependence for lemborexant was tested in a rat physical dependence study and during Phase \2/3\ clinical trials. Based on the data from these studies, HHS concluded that lemborexant lacked physical dependence potential. According to HHS, in the HAP study (presented in Factor 2), lemborexant administration was associated with positive subjective effects as assessed by participant responses to measures of Drug Liking, Overall Drug Liking, Good Drug Effects, High, Stoned, and Take Drug Again. The results indicated that the responses for lemborexant were similar to that of positive control drugs, such as zolpidem and suvorexant. Thus, it is likely that lemborexant can produce psychic dependence similar to that of schedule IV drugs, such as zolpidem and suvorexant.

8. Whether the Substance Is an Immediate Precursor of a Substance Already Controlled Under the CSA

Lemborexant is not an immediate precursor of any controlled substance, as defined in **21 U.S.C. 802(23).**

Conclusion

After considering the scientific and medical evaluation conducted by HHS, HHS's recommendation, and its own eight-factor analysis, DEA has determined that these facts and all

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relevant data constitute substantial evidence of a potential for abuse of lemborexant. As such, DEA hereby schedules lemborexant as a controlled substance under the CSA.

Determination of Appropriate Schedule

The CSA lists the findings required to place a drug or other substance in any particular schedule (I, II, III, IV, or V). **21 U.S.C. 812**(b). After consideration of the analysis and recommendation of the Assistant Secretary for Health of HHS and review of all available data, the Acting Administrator of DEA, pursuant to 21 U.S.C. 812(b)(4), finds that:

1. Lemborexant has a low potential for abuse relative to the drugs or other substances in schedule III.

Lemborexant is a dual orexin receptor antagonist, which produces sedation in human behavioral studies. In the HAP study, therapeutic and supratherapeutic doses of lemborexant produced positive subjective responses such as Drug Liking, Overall Drug Liking, Good Drug Effects, High, Stoned, and Take Drug Again that were statistically significantly greater than those produced by placebo. These responses of lemborexant are similar to those produced by schedule IV drugs suvorexant and zolpidem. Because lemborexant is similar to zolpidem and suvorexant in its abuse potential, lemborexant has a low potential for abuse relative to the drugs and other listed substances in schedule III of the CSA.

2. Lemborexant has a currently accepted medical use in the United States.

FDA recently approved lemborexant oral tablets for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. Thus, lemborexant has a currently accepted medical use in treatment in the United States.

3. Lemborexant may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule III.

As stated by HHS, data from a rat physical dependence study, as well as a physical dependence assessment at the conclusion of the Phase \2/3\ clinical trials, showed that lemborexant did not produce withdrawal symptoms indicative of physical dependence. In the HAP study, lemborexant produced positive subjective responses to measures such as Drug Liking, Overall Drug Liking, Good Drug Effects, High, Stoned, and Take Drug Again that were greater than placebo and similar to that of the schedule IV drugs zolpidem and suvorexant. This data suggests that lemborexant can produce psychic dependence to a similar extent as zolpidem and suvorexant. Thus, abuse of lemborexant may lead to limited psychological dependence relative to the drugs or other substances in schedule III of the CSA.

Based on these findings, the Acting Administrator of DEA concludes that lemborexant warrants control in schedule IV of the CSA. **21 U.S.C. 812**(b)(4).

Requirements for Handling Lemborexant

Lemborexant is subject to the CSA's schedule IV regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, reverse distribution, dispensing, importing, exporting, research, and conduct of instructional activities and chemical analysis with, and possession involving schedule IV substances, including the following:

1. *Registration.* Any person who handles (manufactures, distributes, reverse distributes, dispenses, imports, exports, engages in research, or conducts instructional activities or chemical analysis with, or possesses) lemborexant, or who desires to handle lemborexant, must be registered with DEA to conduct such activities pursuant to **21 U.S.C. 822, 823, 957,** and **958** and in accordance with **21 CFR parts 1301** and **1312.** Any person who currently handles or intends to handle lemborexant and is not registered with DEA must submit an application for registration and may not continue to handle lemborexant, unless DEA has approved that application for registration, pursuant to 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312.

2. *Disposal of stocks.* Any person who does not desire or is not able to maintain a schedule IV registration must surrender all quantities of currently held lemborexant or may transfer all quantities of lemborexant to a person registered with DEA in accordance with **21 CFR part 1317,** in additional to all other applicable Federal, State, local, and tribal laws.

3. *Security.* Lemborexant is subject to schedule III-V security requirements and must be handled and stored in accordance with **21 CFR 1301.71-1301.77.** Non-practitioners handling lemborexant must also comply with the employee screening requirements of **1301.90-1301.93.**

4. *Labeling and Packaging.* All labels, labeling, and packaging for commercial containers of lemborexant must comply with **21 U.S.C. 825** and **958**(e), and be in accordance with **21 CFR part 1302.**

5. *Inventory.* Every DEA registrant who possesses any quantity of lemborexant must take an inventory of lemborexant on hand, pursuant to **21 U.S.C. 827** and **958,** and in accordance with **21 CFR 1304.03, 1304.04,** and **1304.11.**

Any person who becomes registered with DEA to handle lemborexant must take an initial inventory of all stocks of controlled substances (including lemborexant) on hand on the date the registrant first engages in the handling of controlled substances, pursuant to **21 U.S.C. 827** and **958**(e), and in accordance with **21 CFR 1304.03, 1304.04,** and **1304.11.**

After the initial inventory, every DEA registrant must take a new inventory of all stocks of controlled substances (including lemborexant) on hand at least every two years, pursuant to **21 U.S.C. 827** and **958**(e), and in accordance with **21 CFR 1304.03, 1304.04,** and **1304.11.**

6. *Records and Reports.* DEA registrants must maintain records and submit reports for lemborexant, pursuant to **21 U.S.C. 827, 832**(a), and **958**(e), and in accordance with **21 CFR 1301.74**(b) and (c) and **parts 1304, 1312,** and **1317.**

7. *Prescriptions.* All prescriptions for lemborexant, or products containing lemborexant, must comply with **21 U.S.C. 829,** and be issued in accordance with **21 CFR parts 1306** and **1311,** subpart C.

8. *Manufacturing and Distributing.* In addition to the general requirements of the CSA and DEA regulations that are applicable to manufacturers and distributors of schedule IV controlled substances, such registrants should be advised that (consistent with the foregoing considerations) any manufacturing or distribution of lemborexant may only be for the legitimate purposes consistent with the drug's labeling, or for research activities authorized by the FDCA and the CSA.

9. *Importation and Exportation.* All importation and exportation of lemborexant must be in compliance with **21 U.S.C. 952, 953, 957,** and **958,** and in accordance with **21 CFR part 1312.**

10. *Liability.* Any activity involving lemborexant not authorized by, or in violation of, the CSA or its implementing regulations, is unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

Regulatory Analyses

Administrative Procedure Act

Section 553 of the APA (5 U.S.C. 553) generally requires notice and comment

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for rulemakings. However, **21 U.S.C. 811**(j) provides that in cases where a certain new drug is: (1) Approved by HHS, under section 505(c) of the FDCA, and (2) HHS recommends control in CSA schedule II-V, DEA shall issue an interim final rule scheduling the drug within 90 days. As stated in the legal authority section, the 90-day time frame is the later of: (1) The date DEA receives HHS's scientific and medical evaluation/scheduling recommendation, or (2) the date DEA receives notice of the NDA approval by HHS. Additionally, the law specifies that the rulemaking shall become immediately effective as an interim final rule without requiring DEA to demonstrate good cause.

Executive Orders 12866, 13563, and 13771, Regulatory Planning and Review, Improving Regulation and Regulatory Review, and Reducing Regulation and Controlling Regulatory Costs

In accordance with **21 U.S.C. 811**(a) and (j), this scheduling action is subject to formal rulemaking procedures performed "on the record after opportunity for a hearing," which are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth the procedures and criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget (OMB) pursuant to section 3(d)(1) of Executive Order 12866 and the principles reaffirmed in Executive Order 13563.

This interim final rule is not an Executive Order 13771 regulatory action pursuant to Executive Order 12866 and OMB guidance.\6\

\6\ Office of Mgmt. & Budget, Exec. Office of The President, Interim Guidance Implementing Section 2 of the Executive Order of January 30, 2017 Titled "Reducing Regulation and Controlling Regulatory Costs" (Feb. 2, 2017).

Executive Order 12988, Civil Justice Reform

This regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of Executive Order 12988 to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132, Federalism

This rulemaking does not have federalism implications warranting the application of Executive Order 13132. The rule does not have substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government.

Executive Order 13175, Consultation and Coordination With Indian Tribal Governments

This rule does not have tribal implications warranting the application of Executive Order 13175. It does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal government and Indian tribes, or on the distribution of power and responsibilities between the Federal government and Indian tribes.

Regulatory Flexibility Act

The Regulatory Flexibility Act (RFA) (5 U.S.C. 601-612) applies to rules that are subject to notice and comment under section 553(b) of the APA. Under **21 U.S.C. 811**(j), DEA is not required to publish a general notice of proposed rulemaking. Consequently, the RFA does not apply to this interim final rule.

Unfunded Mandates Reform Act of 1995

In accordance with the Unfunded Mandates Reform Act (UMRA) of 1995, 2 U.S.C. 1501 et seq., DEA has determined that this action would not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any 1 year." Therefore, neither a Small Government Agency Plan nor any other action is required under UMRA of 1995.

Paperwork Reduction Act of 1995

This action does not impose a new collection of information requirement under the Paperwork Reduction Act of 1995. 44 U.S.C. 3501-3521. This action would not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Congressional Review Act

This rule is not a major rule as defined by the Congressional Review Act (CRA), 5 U.S.C. 804. This rule will not result in: An annual effect on the economy of $100 million or more; a major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; or significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based companies to compete with foreign-based companies in domestic and export markets. However, pursuant to the CRA, DEA has submitted a copy of this interim final rule to both Houses of Congress and to the Comptroller General.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, DEA amends 21 CFR part 1308 as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

- 1. The authority citation for 21 CFR part 1308 continues to read as follows:

  Authority: 21 U.S.C. 811, 812, 871(b), **956**(b), unless otherwise noted.

- 2. Amend **Sec. 1308.14** by:
- a. Redesignating paragraphs (c)(30) through (c)(56) as (c)(31) through (c)(57); and
- b. Adding new paragraph (c)(30).

The addition reads as follows:

Sec. 1308.14 Schedule IV.

* * * * *

(c) * * *

(30) Lemborexant	2245

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Uttam Dhillon,
Acting Administrator.

[FR Doc. 2020-07089 Filed 4-6-20; 8:45 am]

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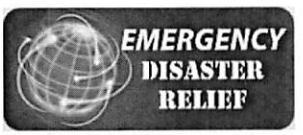

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[Federal Register Volume 85, Number 194 (Tuesday, October 6, 2020)]
[Rules and Regulations]
[Pages 63014-63019]
From the Federal Register Online via the Government Publishing Office [www.gpo.gov]
[FR Doc No: 2020-19313]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-658]

Schedules of Controlled Substances: Placement of Remimazolam in Schedule IV

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Interim final rule with request for comments.

SUMMARY: On July 2, 2020, the U.S. Food and Drug Administration approved a new drug application for BYFAVO (remimazolam) for intravenous use. Remimazolam is chemically known as 4H-imidazol[1,2-a][1,4]benzodiazepine-4-propionic acid, 8-bromo-1-methyl-6-(2-pyridinyl)-(4S)-methyl ester, benzenesulfonate (1:1) and also, methyl 3-[(4S)-8-bromo-1-methyl-6-pyridin-2-yl-4H-imidazo[1,2-a][1,4]benzodiazepin-4yl]propanoate benzenesulfonic acid. The Department of Health and Human Services provided the Drug Enforcement Administration (DEA) with a scheduling recommendation to place remimazolam and its salts in schedule IV of the Controlled Substances Act (CSA). In accordance with the CSA, as amended by the Improving Regulatory Transparency for New Medical Therapies Act, DEA is hereby issuing an interim final rule placing remimazolam, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible, in schedule IV of the CSA.

DATES: The effective date of this rulemaking is October 6, 2020. Interested persons may file written comments on this rulemaking in accordance with **21 U.S.C. 811**(j)(3) and **21CFR 1308.43**(g). Electronic comments must be submitted, and written comments must be postmarked, on or before November 5, 2020. Commenters should be aware that the electronic Federal Docket Management System will not accept comments after 11:59 p.m. Eastern Time on the last day of the comment period.

Interested persons may file a request for hearing or waiver of hearing in accordance with **21 U.S.C. 811**(j)(3) and **21 CFR 1308.44.** Requests for hearing and waivers of an opportunity for a hearing or to participate in a hearing, together with a written statement of position on the matters of fact and law asserted in the hearing, must be received on or before November 5, 2020.

ADDRESSES: To ensure proper handling of comments, please reference "Docket No. DEA-658" on all correspondence, including any attachments.

- *Electronic comments:* The Drug Enforcement Administration (DEA) encourages that all comments be submitted electronically through the Federal eRulemaking Portal, which provides the ability to type short comments directly into the comment field on the web page or attach a file for lengthier comments. Please go to http://www.regulations.gov and follow the online instructions at that site for submitting comments. Upon completion of your submission, you will receive a Comment Tracking Number for your comment. Please be aware that submitted comments are not instantaneously available for public view on Regulations.gov. If you have received a Comment Tracking Number, your comment has been successfully submitted and there is no need to resubmit the same comment.
- *Paper comments:* Paper comments that duplicate the electronic submission are not necessary and are discouraged.

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Should you wish to mail a paper comment in lieu of an electronic comment, it should be sent via regular or express mail to: Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrissette Drive, Springfield, VA 22152.

- *Hearing requests:* All requests for hearing and waivers of participation must be sent to: Drug Enforcement Administration, Attn: Administrator, 8701 Morrissette Drive, Springfield, Virginia 22152. All requests for hearing and waivers of participation should also be sent to: (1) Drug Enforcement Administration, Attn: Hearing Clerk/LJ, 8701 Morrissette Drive, Springfield, Virginia 22152; and (2) Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrissette Drive, Springfield, Virginia 22152.

FOR FURTHER INFORMATION CONTACT: Scott A. Brinks, Regulatory Drafting and Policy Support Section, Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (571) 362-3261.

SUPPLEMENTARY INFORMATION:

Posting of Public Comments

Please note that all comments received are considered part of the public record. They will, unless reasonable cause is given, be made available by the Drug Enforcement Administration (DEA) for public inspection online at http://www.regulations.gov. Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter. The Freedom of Information Act applies to all comments received. If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want it to be made publicly available, you must include the phrase "PERSONAL IDENTIFYING INFORMATION" in the first paragraph of your comment. You must also place all of the personal identifying information you do not want made publicly available in the first paragraph of your comment and identify what information you want redacted. If you want to submit confidential business information as part of your comment, but do not want it to be made publicly available, you must include the phrase "CONFIDENTIAL BUSINESS INFORMATION" in the first paragraph of your comment. You must also prominently identify the confidential business information to be redacted within the comment.

Comments containing personal identifying information and confidential business information identified as directed above will generally be made publicly available in redacted form. If a comment has so much confidential business information or personal identifying information that it cannot be effectively redacted, all or part of that comment may not be made publicly available. Comments posted to http://www.regulations.gov may include any personal identifying information (such as name, address, and phone number) included in the text of your electronic submission that is not identified as directed above as confidential.

An electronic copy of this document and supplemental information, including the complete Department of Health and Human Services (HHS) and DEA eight-factor analyses, to this interim final rule are available at http://www.regulations.gov for easy reference.

Request for Hearing or Waiver of Participation in a Hearing

Pursuant to **21 U.S.C. 811**(a), this action is a formal rulemaking "on the record after opportunity for a hearing." Such proceedings are conducted pursuant to the provisions of the Administrative Procedure Act (APA), 5 U.S.C. 551-559. **21 CFR 1308.41-1308.45; 21 CFR part 1316**, subpart D. Such requests or notices must conform to the requirements of **21 CFR 1308.44**(a) or (b), and **1316.47** or **1316.48**, as applicable, and include a statement of the person's interests in the proceeding and the objections or issues, if any, concerning which the person desires to be heard. Any waiver must conform to the requirements of 21 CFR 1308.44(c) and may include a written statement regarding the interested person's position on the matters of fact and law involved in any hearing.

All requests for a hearing and waivers of participation must be sent to DEA using the address information provided above.

Background and Legal Authority

Under the CSA, as amended in 2015 by the Improving Regulatory Transparency for New Medical Therapies Act (section 2(b) of Pub. L. 114-89), DEA is required to commence an expedited scheduling action with respect to certain new drugs approved by the Food and Drug Administration (FDA). As provided in **21 U.S.C. 811**(j), this expedited scheduling is required where both of the following conditions apply: (1) The Secretary of HHS has advised DEA that a New Drug Application (NDA) has been submitted for a drug that has a stimulant, depressant, or hallucinogenic effect on the central nervous system (CNS), and that it appears that such drug has an abuse potential; and (2) the Secretary of HHS recommends that DEA control the drug in schedule II, III, IV, or V pursuant to 21 U.S.C. 811(a) and (b). In these circumstances, DEA is required to issue an interim final rule controlling the drug within 90 days.

Subsection (j)(2) states that the 90-day timeframe starts the later of (1) the date DEA receives HHS' scientific and medical evaluation/scheduling recommendation, or (2) the date DEA receives notice of the NDA approval by HHS. Subsection (j)(3) specifies that the rulemaking shall become immediately effective as an interim final rule without requiring DEA to demonstrate good cause therefore. Thus, the purpose of subsection (j) is to speed the process by which DEA schedules newly approved drugs that are currently either in schedule I or not controlled (but which have sufficient abuse potential to warrant control) so that such drugs may be marketed without undue delay following FDA approval.\1\

\1\ Given the parameters of subsection (j), in DEA's view, it would not apply to a reformulation of a drug containing a substance currently in schedules II through V for which an NDA has recently been approved.

Subsection (j)(3) further provides that the interim final rule shall give interested persons the opportunity to comment and to request a hearing. After the conclusion of such proceedings, DEA must issue a final rule in accordance with the scheduling criteria of **21 U.S.C. 811**(b) through (d) and **812**(b).

Remimazolam (4H-imidazol[1,2-a][1,4]benzodiazepine-4-propionic acid, 8-bromo-1-methyl-6-(2-pyridinyl)-(4S)-methyl ester, benzenesulfonate (1:1) or methyl 3-[(4S)-8-bromo-1-methyl-6-pyridin-2-yl-4H-imidazo[1,2-a][1,4]benzodiazepin-4yl]propanoate benzenesulfonic acid), is a new molecular entity with CNS depressant properties. Remimazolam is an agonist at gamma-aminobutyric acid subtype A (GABAA) receptors. On April 5, 2019, Cosmo Technologies, Ltd. (Sponsor) submitted an NDA for BYFAVO (remimazolam) to FDA with a proposed dose of 5.0 mg (intravenous; i.v.) with supplemental doses of 2.6 mg (i.v.). On July 2, 2020, DEA received notification that FDA, on the same date, approved the NDA for BYFAVO (remimazolam), under section 505(c) of the Federal Food, Drug, and Cosmetic Act (FDCA), to be used as an i.v. treatment for the induction and maintenance of

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procedural sedation in adults undergoing procedures lasting 30 minutes or less. In January 2020, remimazolam was approved for marketing in Japan for general anesthesia.\2\

\2\ Keam SJ (2020). Remimazolam: First Approval. Drugs; 80(6):625-633.

Determination To Schedule Remimazolam

On July 10, 2020, DEA received from HHS a scientific and medical evaluation (dated April 15, 2020) entitled "Basis for the Recommendation to Control Remimazolam and its Salts in Schedule IV of the Controlled Substances Act" and a scheduling recommendation. Pursuant to **21 U.S.C. 811**(b) and (c), this document contained an eight-factor analysis of the abuse potential, legitimate medical use, and dependence liability of remimazolam, along with HHS's recommendation to control remimazolam and its salts under schedule IV of the CSA.

In response, DEA reviewed the scientific and medical evaluation and scheduling recommendation provided by HHS, along with all other relevant data, and completed its own eight-factor review pursuant to **21 U.S.C. 811**(c). DEA concluded that remimazolam meets the **21 U.S.C. 812**(b)(4) criteria for placement in schedule IV of the CSA.

Pursuant to **subsection 811**(j), and based on HHS' recommendation, NDA approval by HHS/FDA, and DEA's determination, DEA is issuing this interim final rule to schedule remimazolam as a schedule IV controlled substance under the CSA.

Included below is a brief summary of each factor as analyzed by HHS and DEA, and as considered by DEA in its scheduling action. Please note that both DEA and HHS analyses are available in their entirety under "Supporting Documents" in the public docket for this interim final rule at http://www.regulations.gov, under Docket Number "DEA-658." Full analysis of, and citations to, the information referenced in the summary may also be found in the supporting and related material.

1. Its Actual or Relative Potential for Abuse

Remimazolam is a new molecular entity that has not been marketed in the United States, and was approved in Japan for general anesthesia in January 2020. Evidence regarding its diversion, illicit manufacturing, or deliberate ingestions is lacking. DEA notes that there are no reports for remimazolam in the National Forensic Laboratory Information System (NFLIS),\3\ which collects drug cases submitted to and analyzed by state and local forensic laboratories. There were also no reports in STARLIMS,\4\ DEA's laboratory drug evidence data system of record.

\3\ NFLIS represents an important resource in monitoring illicit drug trafficking, including the diversion of legally manufactured pharmaceuticals into illegal markets. NFLIS is a comprehensive information system that includes data from forensic laboratories that handle more than 96% of an estimated 1.0 million distinct annual State and local drug analysis cases. NFLIS includes drug chemistry results from completed analyses only. While NFLIS data is not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. See 76 FR 77330, 77332, Dec. 12, 2011. NFLIS data were queried April 23, 2020.

\4\ On October 1, 2014, DEA implemented STARLIMS (a web-based, commercial laboratory information management system) to replace the System to Retrieve Information from Drug Evidence (STRIDE) as its laboratory drug evidence data system of record. DEA laboratory data submitted after September 30, 2014, are reposited in STARLIMS. STARLIMS data were queried May 5, 2020.

As stated by HHS, remimazolam is so related in action to depressant drugs such as benzodiazepines in schedule IV that it is reasonable to assume that there may be comparable diversions from legitimate channels, use contrary to or without medical advice, and capability of creating hazards to the users and to the safety of the community. Preclinical and clinical studies show that remimazolam has similar pharmacological mechanism of action as an agonist at the GABAA receptors as midazolam. Data gathered from general behavior studies indicate remimazolam produces a sedative effect, and similar abuse-related effects in humans and in animal studies to those of midazolam, a schedule IV depressant. It is likely that remimazolam has similar abuse potential and is likely to be abused for its depressant effects, contrary to medical advice.

2. Scientific Evidence of Its Pharmacological Effects, if Known

Remimazolam shares similar pharmacological mechanism of action via GABAA receptor agonism as schedule IV benzodiazepines, such as midazolam. The GABAA receptor is a ligand-gated chloride ion channel consisting of five subunits and a central chloride channel. Benzodiazepines enhance the opening of the ligand-gated chloride channel and the influx of chloride.

Remimazolam, similar to schedule IV benzodiazepines, has sedative activity in animals. Acute administration of remimazolam in rats elicited dose-dependent behaviors indicative of sedative and muscle relaxation properties of the drug. In a drug discrimination study using male rats previously trained to discriminate midazolam, remimazolam produced interoceptive cues that are similar to those of midazolam. Remimazolam was self-administered variably based on session duration. In the shorter-access paradigm (two-hour sessions), only two of four monkeys tested self-administered remimazolam, whereas for the longer-access paradigm (24-hour sessions), all four monkeys self-administered remimazolam at a rate higher than placebo and pentobarbital, the reference drug (a schedule II or III depressant).\5\

\5\ The HHS review of remimazolam incorrectly stated that pentobarbital was a schedule IV substance. FDA/Controlled Substance Staff through an email correspondence confirmed that it was an inadvertent error in the HHS review. Pentobarbital is currently controlled as schedule II (**21 CFR 1308.12**(e)), or as schedule III if any material, compound, mixture, or preparation containing any quantity of pentobarbital having a depressant effect on the central nervous system (**21 CFR 1308.13**(c)(1)), or any suppository dosage form and its salts that are approved by FDA for marketing only as a suppository (21 CFR 1308.13(c)(2)).

In human abuse potential studies, remimazolam, in agreement with its mechanism of action as a GABAA receptor agonist, produced subjective responses and abuse-related neuropharmacology profile similar to that of midazolam, a schedule IV depressant.

3. The State of Current Scientific Knowledge Regarding the Drug or Other Substance

Remimazolam is a new molecular entity. It is chemically known as 4H-imidazol[1,2- a][1,4]benzodiazepine-4- propionic acid, 8-bromo-1-methyl-6-(2-pyridinyl)-(4S)-methyl ester, benzenesulfonate (1:1) and also as methyl 3-[(4S)-8-bromo-1-methyl-6-pyridin-2-yl-4H-imidazo[1,2-a][1,4]benzodiazepin-4yl]propanoate benzenesulfonic acid. It is a white to off-white powder that is freely soluble in water. In preclinical studies, remimazolam, an ester based drug, is rapidly hydrolyzed by tissue esterases, primarily in the liver by carboxylesterase-1, and results in one inactive metabolite. In humans, acute administration of the proposed therapeutic dose (5 mg, i.v.) of remimazolam resulted in rapid onset sedative effects (one to three minutes), fast time to maximal plasma concentration (Tmax, nine minutes), and a short half-life (twenty minutes).

4. Its History and Current Pattern of Abuse

There is no information on the history and current pattern of abuse for

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remimazolam, since it has not been marketed, legally or illegally, in the United States, and only recently in Japan. HHS notes that the abuse potential of remimazolam is similar to that of schedule IV benzodiazepines. Therefore, if remimazolam were available for marketing, it is likely to be abused in a manner similar to schedule IV benzodiazepines, such as midazolam.

DEA conducted a search of NFLIS and STARLIMS databases for remimazolam encounters. No records of encounters by law enforcement were identified in these databases, which is consistent with the fact that remimazolam is a new molecular entity.

The pharmacological mechanism of action of remimazolam through GABAA receptor agonism suggests that its pattern of abuse would be similar to schedule IV depressants with a similar mechanism of action, such as midazolam.

5. The Scope, Duration, and Significance of Abuse

Remimazolam is not marketed in the United States, legally or illegally, and marketed only recently in Japan. However, because of remimazolam's pharmacological similarities to schedule IV benzodiazepines, remimazolam, similar to these schedule IV substances, is likely to be abused when available in the market.

6. What, If Any, Risk There Is To the Public Health

According to HHS, the public health risk associated with remimazolam is due to its abuse potential and is largely borne by the individual. Data from preclinical and clinical studies showed that remimazolam has abuse potential similar to that of the schedule IV depressant midazolam. In clinical studies when remimazolam was given to healthy individuals, adverse events such as euphoric mood and somnolence occurred; thus, remimazolam produced rewarding and depressant effects, as would be expected from a benzodiazepine. Therefore, upon availability for marketing, it is likely to pose a public health risk to a degree similar to schedule IV benzodiazepines, such as midazolam.

7. Its Psychic or Physiological Dependence Liability

As described in the HHS review, the Sponsor conducted a study related to physical dependence liability produced by remimazolam in six cynomolgus monkeys (0.5, 0.75, and 1.0 mg/kg/h, continuous i.v. infusion for 28 days) and psychic dependence liability in 39 humans (doses tested 5 and 10 mg, i.v.).

During extended daily dosing administrations lasting a period of 28 days, all monkeys showed depressant signs, such as ataxia, slowed motion, and hyporeactivity. During the discontinuation phase, all monkeys showed withdrawal signs including: Facial apprehension, hyperirritability, piloerection, muscle rigidity, retching and vomiting, tremors, restlessness, and impaired motor activity. Decreases in food consumption and body weights were also observed. Severe withdrawal symptoms such as dissociation from the environment, systemic convulsions, and continuously prone position for 25 hours were observed in one monkey, and remimazolam administration lessened this withdrawal syndrome in this monkey. HHS concluded that remimazolam produces physical dependence, as evidenced by the withdrawal syndrome observed after its chronic administration was discontinued.

Remimazolam produced positive subjective responses to ratings of Drug Liking, Overall Drug Liking, Good Drug Effects, and Take Drug Again in a human abuse potential study. The responses were significantly higher than the placebo and similar to midazolam, a schedule IV depressant. HHS concluded that remimazolam can produce psychic dependence to a similar extent as midazolam.

8. Whether the Substance is an Immediate Precursor of a Substance Already Controlled Under the CSA

Remimazolam is not an immediate precursor of any controlled substance, as defined by **21 U.S.C. 802**(23).

Conclusion: After considering the scientific and medical evaluation conducted by HHS, HHS's recommendation, and its own eight-factor analysis, DEA has determined that these facts and all relevant data constitute substantial evidence of potential for abuse of remimazolam. As such, DEA hereby schedules remimazolam as a controlled substance under the CSA.

Determination of Appropriate Schedule

The CSA lists the findings required to place a drug or other substance in any particular schedule (I, II, III, IV, or V). **21 U.S.C. 812**(b). After consideration of the analysis and recommendation of the Assistant Secretary for Health of HHS and review of all available data, the Acting Administrator of DEA, pursuant to 21 U.S.C. 812(b)(4), finds that:

1. Remimazolam Has a Low Potential for Abuse Relative to the Drugs or Other Substances in Schedule III.

Remimazolam, similar to that of the schedule IV drug midazolam, is an agonist at GABAA receptors. Remimazolam produced depressant effects in general behavior assessments, and generalized to midazolam (schedule IV) in a drug discrimination study in animals, demonstrating it has GABAA receptor agonist properties. In a human abuse potential study, remimazolam at the therapeutic and supra-therapeutic doses produced positive subjective responses such as Drug Liking, Overall Drug Liking, Good Drug Effects, and Take Drug Again similar to those of midazolam (schedule IV) and significantly higher than placebo. Furthermore, data from other clinical studies show that remimazolam produced abuse-related adverse events, namely euphoria and somnolence. Because remimazolam is similar to midazolam (schedule IV) in its abuse potential, remimazolam has a lower potential for abuse relative to the drugs or other substances in schedule III.

2. Remimazolam Has a Currently Accepted Medical Use in the United States.

FDA recently approved the NDA for BYFAVO (remimazolam) injection for use in the induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 minutes or less. Thus, remimazolam has a currently accepted medical use for treatment in the United States.

3. Remimazolam May Lead To Limited Physical Dependence or Psychological Dependence Relative to the Drugs or Other Substances in Schedule III.

Remimazolam shares a similar pharmacology profile with benzodiazepine drugs. Abrupt discontinuation of benzodiazepines is associated with withdrawal symptoms. Remimazolam produced withdrawal symptoms after abrupt discontinuation in monkeys, indicative of physical dependence, similar to that of benzodiazepines. In addition, remimazolam produced positive subjective responses and euphoria-related adverse events in a human abuse potential study. It is likely that remimazolam can produce psychic dependence similar to midazolam. Thus, abuse of remimazolam may lead to limited physical or psychological dependence relative to the drugs or other substances in schedule III of the CSA.

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Based on these findings, the Acting Administrator of DEA concludes that remimazolam warrants control in schedule IV of the CSA. **21 U.S.C. 812**(b)(4).

Requirements for Handling Remimazolam

Remimazolam is subject to the CSA's schedule IV regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, reverse distribution, dispensing, importing, exporting, research, and conduct of instructional activities and chemical analysis with, and possession involving schedule IV substances, including the following:

1. *Registration.* Any person who intends to handle (manufactures, distributes, reverse distributes, dispenses, imports, exports, engages in research, or conducts instructional activities or chemical analysis with, or possesses) remimazolam, or who desires to handle remimazolam, must be registered with DEA to conduct such activities pursuant to **21 U.S.C. 822, 823, 957,** and **958** and in accordance with **21 CFR parts 1301** and **1312.** Any person who currently handles or intends to handle remimazolam and is not registered with DEA must submit an application for registration and may not continue to handle remimazolam unless DEA has approved that application for registration, pursuant to 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312.

2. *Disposal of stocks.* Any person who does not desire or is not able to maintain a schedule IV registration must surrender all quantities of currently held remimazolam or may transfer all quantities of remimazolam to a person registered with DEA in accordance with **21 CFR part 1317,** in additional to all other applicable Federal, State, local, and tribal laws.

3. *Security.* Remimazolam is subject to schedule III-V security requirements and must be handled and stored in accordance with **21 CFR 1301.71-1301.77.** Non-practitioners handling remimazolam must also comply with the employee screening requirements of **21 CFR 1301.90-1301.93.**

4. *Labeling and Packaging.* All labels, labeling, and packaging for commercial containers of remimazolam must comply with **21 U.S.C. 825** and **958**(e), and be in accordance with **21 CFR part 1302.**

5. *Inventory.* Every DEA registrant who possesses any quantity of remimazolam must take an inventory of remimazolam on hand, pursuant to **21 U.S.C. 827** and **958**, and in accordance with **21 CFR 1304.03, 1304.04,** and **1304.11.**

Any person who becomes registered with DEA to handle remimazolam must take an initial inventory of all stocks of controlled substances (including remimazolam) on hand on the date the registrant first engages in the handling of controlled substances, pursuant to **21 U.S.C. 827** and **958**(e), and in accordance with **21 CFR 1304.03, 1304.04,** and **1304.11.**

After the initial inventory, every DEA registrant must take a new inventory of all stocks of controlled substances (including remimazolam) on hand every two years, pursuant to **21 U.S.C. 827** and **958**(e), and in accordance with **21 CFR 1304.03, 1304.04,** and **1304.11.**

6. *Records and Reports.* DEA registrants must maintain records and submit reports for remimazolam, pursuant to **21 U.S.C. 827, 832**(a), and **958**(e), and in accordance with **21 CFR 1301.74**(b) and (c) and **parts 1304, 1312,** and **1317.**

7. *Prescriptions.* All prescriptions for remimazolam, or products containing remimazolam, must comply with **21 U.S.C. 829,** and be issued in accordance with **21 CFR parts 1306** and **1311,** subpart C.

8. *Manufacturing and Distributing.* In addition to the general requirements of the CSA and DEA regulations that are applicable to manufacturers and distributors of schedule IV controlled substances, such registrants should be advised that (consistent with the foregoing considerations) any manufacturing or distribution of remimazolam may only be for the legitimate purposes consistent with the drug's labeling, or for research activities authorized by the FDCA and CSA.

9. *Importation and Exportation.* All importation and exportation of remimazolam must be in compliance with **21 U.S.C. 952, 953, 957,** and **958,** and in accordance with **21 CFR part 1312.**

10. *Liability.* Any activity involving remimazolam not authorized by, or in violation of, the CSA or its implementing regulations, is unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

Regulatory Analyses

Administrative Procedure Act

Section 553 of the APA (5 U.S.C. 553) generally requires notice and comment for rulemakings. However, **21 U.S.C. 811**(j) provides that in cases where a certain new drug is (1) approved by HHS, under section 505(c) of the FDCA and (2) HHS recommends control in CSA schedule II-V, DEA shall issue an interim final rule scheduling the drug within 90 days. As stated in the legal authority section, the 90-day time frame is the later of: (1) the date DEA receives HHS's scientific and medical evaluation/scheduling recommendation, or (2) the date DEA receives notice of the NDA approval by HHS. Additionally, subsection (j) specifies that the rulemaking shall become immediately effective as an interim final rule without requiring DEA to demonstrate good cause.

Executive Orders 12866, 13563, and 13771, Regulatory Planning and Review, Improving Regulation and Regulatory Review, and Reducing Regulation and Controlling Regulatory Costs

In accordance with **21 U.S.C. 811**(a) and (j), this scheduling action is subject to formal rulemaking procedures performed "on the record after opportunity for a hearing," which are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth the procedures and criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget (OMB) pursuant to section 3(d)(1) of Executive Order (E.O.) 12866 and the principles reaffirmed in E.O. 13563.

This interim final rule is not an E.O. 13771 regulatory action pursuant to E.O. 12866 and OMB guidance.\6\

\6\ Office of Mgmt. & Budget, Exec. Office of The President, Interim Guidance Implementing Section 2 of the Executive Order of January 30, 2017 Titled "Reducing Regulation and Controlling Regulatory Costs" (Feb. 2, 2017).

Executive Order 12988, Civil Justice Reform

This regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of E.O. 12988 to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132, Federalism

This rulemaking does not have federalism implications warranting the application of E.O. 13132. The rule does not have substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government.

Executive Order 13175, Consultation and Coordination With Indian Tribal Governments

This rule does not have tribal implications warranting the application of E.O. 13175. It does not have

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substantial direct effects on one or more Indian tribes, on the relationship between the Federal government and Indian tribes, or on the distribution of power and responsibilities between the Federal government and Indian tribes.

Regulatory Flexibility Act

The Regulatory Flexibility Act (RFA) (5 U.S.C. 601-612) applies to rules that are subject to notice and comment under section 553(b) of the APA. Under **21 U.S.C. 811**(j), DEA is not required to publish a general notice of proposed rulemaking. Consequently, the RFA does not apply to this interim final rule.

Unfunded Mandates Reform Act of 1995

In accordance with the Unfunded Mandates Reform Act (UMRA) of 1995, 2 U.S.C. 1501 et seq., DEA has determined that this action would not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million or more (adjusted annually for inflation) in any 1 year." Therefore, neither a Small Government Agency Plan nor any other action is required under UMRA of 1995.

Paperwork Reduction Act of 1995

This action does not impose a new collection of information requirement under the Paperwork Reduction Act of 1995. 44 U.S.C. 3501-3521. This action would not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Congressional Review Act

This rule is not a major rule as defined by the Congressional Review Act (CRA), 5 U.S.C. 804. This rule will not result in: An annual effect on the economy of $100,000,000 or more; a major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; or significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based companies to compete with foreign-based companies in domestic and export markets. However, pursuant to the CRA, DEA has submitted a copy of this interim final rule to both Houses of Congress and to the Comptroller General.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, DEA amends 21 CFR part 1308 as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

- 1. The authority citation for 21 CFR part 1308 continues to read as follows:

Authority: 21 U.S.C. 811, 812, 871(b), **956**(b) unless otherwise noted.

- 2. In **Sec. 1308.14**:
- a. Redesignate paragraphs (c)(51) through (c)(57) as (c)(52) through (c)(58); and
- b. Add new paragraph (c)(51).

The addition reads as follows:

Sec. 1308.14 Schedule IV.

* * * * *

(c) * * *

(51) Remimazolam	2846

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Timothy J. Shea,
Acting Administrator.

[FR Doc. 2020-19313 Filed 10-5-20; 8:45 am]

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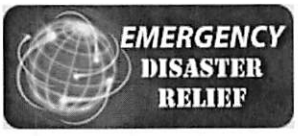

Rules - 2020

[Federal Register Volume 85, Number 4 (Tuesday, January 7, 2020)]
[Rules and Regulations]
[Pages 643-645]
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[FR Doc No: 2019-27955]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-504]

Schedules of Controlled Substances: Placement of Solriamfetol in Schedule IV

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final rule.

SUMMARY: This final rule adopts, without change, an interim final rule with request for comments published in the Federal Register on June 17, 2019, placing solriamfetol (2-amino-3-phenylpropyl carbamate), including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible, in schedule IV of the Controlled Substances Act. With the issuance of this final rule, the Drug Enforcement Administration maintains solriamfetol, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible, in schedule IV of the CSA.

DATES: The effective date of this final rulemaking is January 7, 2020.

FOR FURTHER INFORMATION CONTACT: Scott A. Brinks, Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (202) 598-6812.

SUPPLEMENTARY INFORMATION:

Background and Legal Authority

The Improving Regulatory Transparency for New Medical Therapies Act (Pub. L. 114-89) was signed into law on November 25, 2015. This law amended the Controlled Substances Act (CSA) and states that in cases where the Drug Enforcement Administration (DEA) receives notification from The Department of Health and Human Services (HHS) that the Secretary has approved an application under section 505(c) of the Federal Food, Drug, and Cosmetic Act (FDCA), the DEA is required to issue an interim final rule, with opportunity for public comment and to request a hearing, controlling the drug not later than 90 days after receiving such notification from HHS and subsequently to issue a final rule. **21 U.S.C. 811**(j). When controlling a drug pursuant to section 811(j), the DEA must apply the scheduling criteria of subsections 811(b), (c), and (d) and **section 812**(b). 21 U.S.C. 811(j)(3).

Solriamfetol (2-amino-3-phenylpropyl carbamate) is a new molecular entity with central nervous system (CNS) stimulant properties. Solriamfetol primarily acts as a dopamine and norepinephrine reuptake inhibitor and does not bind to any other receptors that are typically associated with abuse, such as opioid or cannabinoid receptors, GABAergic, and other ion channels. On December 20, 2017, Jazz Pharmaceuticals, Inc. (Sponsor) submitted a new drug application (NDA) to the Food and Drug Administration (FDA) for SUNOSI (solriamfetol) 75 and 150 mg oral tablets. On March 19, 2019, DEA received from HHS a scientific and medical evaluation document (dated March 8, 2019) prepared by the FDA related to solriamfetol. Pursuant to **21 U.S.C. 811**(b), this document contained an eight-factor analysis of the abuse potential of solriamfetol, along with HHS' recommendation to control solriamfetol under schedule IV of the CSA. Subsequently, on March 20, 2019, the DEA received notification that the FDA, on that same date, approved the NDA for SUNOSI (solriamfetol), under section 505(c) of the FDCA, to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA).

On June 17, 2019, the DEA published an interim final rule [84 FR 27943] to make solriamfetol (including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible) a schedule IV controlled substance. Interested persons were provided a 30 day comment period in which to submit comments on this rulemaking in accordance with **21 U.S.C. 811**(j)(3) and **21 CFR 1308.43**(g). In addition, interested persons were provided an opportunity to file a request for hearing or waiver of hearing pursuant to 21 U.S.C. 811(j)(3) and **21 CFR 1308.44**. The deadline for submitting comments or requests for hearing/waiver of hearing was July 17, 2019. The DEA received one comment and did not receive any requests for hearing or waiver of hearing.

Comments Received

In response to the interim final rule, the DEA received one comment. The commenter indicated that all clinical studies on solriamfetol are supported by the sponsor of the NDA for solriamfetol and thus subject to conflicts of interests. This commenter further stated that long-term adverse health effects (including adverse effects on the cardiovascular system) of solriamfetol have not been studied and such effects need to be considered.

DEA Response: The comment relating to the alleged conflicts of interests as a result of financial support of the clinical studies by the sponsor of the NDA and the long-term toxicity of solriamfetol are related to the FDA approval process (such as weighing the benefits versus risks of approving the drug for the proposed indication) and are outside of the scope of this rulemaking because they do not relate to the factors determinative of control of a substance (**21 U.S.C. 811**(c)). The DEA notes that the FDA approved an NDA for solriamfetol and provided the DEA with a scheduling recommendation for solriamfetol. The scheduling recommendation by HHS and its notification to DEA regarding the FDA approval of the NDA initiated the DEA review and scheduling action. As stated in the interim final rule, after careful consideration of data from preclinical and clinical studies, the DEA concurred with the HHS recommendation that solriamfetol has abuse potential comparable to other schedule IV stimulants and therefore supported--and continues to support through this final rule--placement of solriamfetol in schedule IV under the CSA.

Based on the rationale set forth in the interim final rule, the DEA adopts the interim final rule, without change.

Requirements for Handling Solriamfetol

As indicated above, solriamfetol has been a schedule IV controlled substance by virtue of the interim final rule issued by DEA in June 2019. Thus, this final rule does not alter the regulatory requirements applicable to handlers of solriamfetol that have been in place since that time. Nonetheless, for informational purposes, we restate here those requirements. Solriamfetol is subject to the CSA's schedule IV regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, reverse distribution, dispensing, importing, exporting, research, and conduct of instructional activities and chemical analysis with, and possession involving schedule IV substances, including, but not limited to, the following:

1. *Registration.* Any person who handles (manufactures, distributes, reverse distributes, dispenses, imports, exports, engages in research, or conducts instructional activities or chemical analysis with, or possesses) solriamfetol, or who desires to handle solriamfetol, must be registered with the DEA to conduct such activities

pursuant to **21 U.S.C. 822, 823, 957,** and **958** and

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in accordance with **21 CFR parts 1301** and **1312.** Any person who intends to handle solriamfetol, and is not registered with the DEA, must submit an application for registration and may not handle solriamfetol, unless the DEA approves that application for registration, pursuant to **21 U.S.C. 822, 823, 957,** and **958,** and in accordance with 21 CFR parts 1301 and 1312.

2. *Disposal of stocks.* Any person who obtains a schedule IV registration to handle solriamfetol but who subsequently does not desire or is not able to maintain such registration must surrender all quantities of solriamfetol, or may transfer all quantities of solriamfetol to a person registered with the DEA in accordance with **21 CFR part 1317,** in addition to all other applicable federal, state, local, and tribal laws.

3. *Security.* Solriamfetol is subject to schedule III-V security requirements and must be handled and stored in accordance with **21 CFR 1301.71-1301.93.**

4. *Labeling and Packaging.* All labels, labeling, and packaging for commercial containers of solriamfetol must comply with **21 U.S.C. 825** and **958(e),** and be in accordance with **21 CFR part 1302.**

5. *Inventory.* Every DEA registrant who possesses any quantity of solriamfetol was required to keep an inventory of solriamfetol on hand, as of June 17, 2019, pursuant to **21 U.S.C. 827** and **958(e),** and in accordance with **21 CFR 1304.03, 1304.04,** and **1304.11.**

6. *Records and Reports.* DEA registrants must maintain records and submit reports for solriamfetol, or products containing solriamfetol, pursuant to **21 U.S.C. 827** and **958(e),** and in accordance with **21 CFR parts 1304, 1312,** and **1317.**

7. *Prescriptions.* All prescriptions for solriamfetol or products containing solriamfetol must comply with **21 U.S.C. 829,** and be issued in accordance with **21 CFR parts 1306** and **1311,** subpart C.

8. *Manufacturing and Distributing.* In addition to the general requirements of the CSA and DEA regulations that are applicable to manufacturers and distributors of schedule IV controlled substances, such registrants should be advised that (consistent with the foregoing considerations) any manufacturing or distribution of solriamfetol may only be for the legitimate purposes consistent with the drug's labeling, or for research activities authorized by the Federal Food, Drug, and Cosmetic Act and the CSA.

9. *Importation and Exportation.* All importation and exportation of solriamfetol must be in compliance with **21 U.S.C. 952, 953, 957,** and **958,** and in accordance with **21 CFR part 1312.**

10. *Liability.* Any activity involving solriamfetol not authorized by, or in violation of, the CSA or its implementing regulations, is unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

Regulatory Analyses

Administrative Procedure Act

This final rule, without change, affirms the amendment made by the interim final rule that is already in effect. Section 553 of the Administrative Procedure Act (APA) (5 U.S.C. 553) generally requires notice and comment for rulemakings. However, **21 U.S.C. 811** provides that in cases where a new drug is (1) approved by HHS and (2) HHS recommends control in CSA schedule II-V, the DEA shall issue an interim final rule scheduling the drug within 90 days. Additionally, the law specifies that the rulemaking shall become immediately effective as an interim final rule without requiring the DEA to demonstrate good cause. The DEA issued an interim final rule on June 17, 2019 and solicited public comments on that rule. Section 811 further states that after giving interested persons the opportunity to comment and to request a hearing, "the Attorney General shall issue a final rule in accordance with the scheduling criteria of subsections (b), (c), and (d) of this section and **section 812**(b) of" the CSA. 21 U.S.C. 811(j)(3). The DEA is now responding to the comment submitted by the public and issuing the final rule, in conformity with the APA and the procedure required by 21 U.S.C. 811.

Executive Orders 12866, 13563, and 13771, Regulatory Planning and Review, Improving Regulation and Regulatory Review, and Reducing Regulatory and Controlling Regulatory Costs

In accordance with **21 U.S.C. 811**(a) and (j), this scheduling action is subject to formal rulemaking procedures performed "on the record after opportunity for a hearing," which are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth the procedures and criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget (OMB) pursuant to section 3(d)(1) of Executive Order 12866 and the principles reaffirmed in Executive Order 13563.

This final rule is not an Executive Order 13771 regulatory action pursuant to Executive Order 12866 and OMB guidance.\1\

\1\ Office of Mgmt. & Budget, Exec. Office of The President, Interim Guidance Implementing Section 2 of the Executive Order of January 30, 2017 Titled "Reducing Regulation and Controlling Regulatory Costs" (Feb. 2, 2017).

Executive Order 12988, Civil Justice Reform

This regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of Executive Order 12988 to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132, Federalism

This final rule does not have federalism implications warranting the application of Executive Order 13132. The final rule does not have substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government.

Executive Order 13175, Consultation and Coordination With Indian Tribal Governments

This final rule does not have tribal implications warranting the application of Executive Order 13175. It does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal Government and Indian tribes, or on the distribution of power and responsibilities between the Federal Government and Indian tribes.

Regulatory Flexibility Act

The Regulatory Flexibility Act (RFA) (5 U.S.C. 601-612) applies to rules that are subject to notice and comment under section 553(b) of the APA. Under **21 U.S.C. 811(j),** the DEA was not required to publish a general notice of proposed rulemaking prior to this final rule. Consequently, the RFA does not apply.

Unfunded Mandates Reform Act of 1995

In accordance with the Unfunded Mandates Reform Act (UMRA) of 1995, 2 U.S.C. 1501 et seq., the DEA has determined and certifies that this action would not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted for inflation) in any one year." Therefore, neither a Small Government Agency Plan nor any other action is required under UMRA of 1995.

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Paperwork Reduction Act of 1995

This action does not impose a new collection of information requirement under the Paperwork Reduction Act of 1995. 44 U.S.C. 3501-3521. This action would not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Congressional Review Act

This final rule is not a major rule as defined by the Congressional Review Act (CRA), 5 U.S.C. 804. This rule will not result in an annual effect on the economy of $100,000,000 or more; a major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; or significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of U.S.-based companies to compete with foreign based companies in domestic and export markets. However, pursuant to the CRA, the DEA has submitted a copy of this final rule to both Houses of Congress and to the Comptroller General.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

PART 1308--**SCHEDULES OF CONTROLLED SUBSTANCES**

- Accordingly, the interim final rule amending 21 CFR part 1308, which published on June 17, 2019 (**84 FR 27943**), is adopted as a final rule without change.

Dated: December 17, 2019.

Uttam Dhillon,
Acting Administrator.

[FR Doc. 2019-27955 Filed 1-6-20; 8:45 am]

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Rules - 2020

[Federal Register Volume 85, Number 162 (Thursday, August 20, 2020)]
[Rules and Regulations]
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From the Federal Register Online via the Government Publishing Office [www.gpo.gov]
[FR Doc No: 2020-17357]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-581]

Schedules of Controlled Substances: Placement of Cenobamate in Schedule V

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final rule.

SUMMARY: This final rule adopts, without change, an interim final rule with request for comments published in the Federal Register on March 10, 2020, placing cenobamate [(1R)-1-(2-chlorophenyl)-2-(tetrazol-2-yl)ethyl] carbamate, including its salts, in schedule V of the Controlled Substances Act (CSA). With the issuance of this final rule, the Drug Enforcement Administration maintains cenobamate, including its salts, in schedule V of the CSA.

DATES: The effective date of this rulemaking is August 20, 2020.

FOR FURTHER INFORMATION CONTACT: Scott A. Brinks, Regulatory Drafting and Policy Support Section, Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (571) 362-3261.

SUPPLEMENTARY INFORMATION:

Background and Legal Authority

Under the Controlled Substances Act (CSA), as amended in 2015 by the Improving Regulatory Transparency for New Medical Therapies Act (Pub. L. 114-89), when the Drug Enforcement Administration (DEA) receives notification from the Department of Health and Human Services (HHS) that the Secretary has approved a certain new drug and HHS recommends control in the CSA schedule II-V, DEA is required to issue an interim final rule, with opportunity for public comment and to request a hearing, controlling the drug within a specified 90-day timeframe and subsequently to issue a final rule. **21 U.S.C. 811**(j). When controlling a drug pursuant to subsection (j), DEA must apply the scheduling criteria of 21 U.S.C. 811 (b) through (d) and **812**(b). 21 U.S.C. 811(j)(3).

On March 10, 2020, DEA published an interim final rule in the Federal Register to make cenobamate (including its salts) a schedule V controlled substance. 85 FR 13741. The interim final rule provided an opportunity for interested persons to submit comments, as well as file a request for hearing or waiver of hearing, on or before April 9, 2020. DEA received two comments and did not receive any requests for hearing or waiver of hearing.

Comments Received

In response to the interim final rule, DEA received two comments. One comment was blank and the second comment was not related to the scheduling of cenobamate. Therefore, DEA has no responses to those comments.

Based on the rationale set forth in the interim final rule, DEA adopts the interim final rule, without change.

Requirements for Handling Cenobamate

As indicated above, cenobamate has been a schedule V controlled substance by virtue of an interim final rule issued by DEA in March 2020. Thus, this final rule does not alter the regulatory requirements applicable to handlers of cenobamate that have been in place since that time. Nonetheless, for informational purposes, we restate here those requirements. Cenobamate is subject to the CSA's schedule V regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, reverse distribution, dispensing, importing, exporting, research, and conduct of instructional activities and chemical analysis with, and possession involving schedule V substances, including the following:

1. *Registration.* Any person who handles (manufactures, distributes, reverse distributes, dispenses, imports, exports, engages in research, or conducts instructional activities or chemical analysis with, or possesses) cenobamate, or who desires to handle cenobamate, must be registered with DEA to conduct such activities pursuant to **21 U.S.C. 822**, **823**, **957**, and **958** and in accordance with **21 CFR parts 1301** and **1312**. Any person who intends to handle cenobamate, and is not registered with DEA, must submit an application for registration and may not continue to handle cenobamate, unless DEA has approved that application for registration, pursuant to 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312.

2. *Disposal of stocks.* Any person who obtains a schedule V registration to handle cenobamate and subsequently determines they are no longer willing or able to maintain such registration must surrender all quantities of currently held cenobamate, or may transfer all quantities of cenobamate to a person registered with DEA in accordance with **21 CFR part 1317**, in addition to all other applicable Federal, State, local, and tribal laws.

3. *Security.* Cenobamate is subject to schedule III-V security requirements and must be handled and stored in accordance with **21 CFR 1301.71-1301.93**. Non-practitioners handling cenobamate must also comply with the employee screening requirements of **21 CFR 1301.90-1301.93**.

4. *Labeling and Packaging.* All labels, labeling, and packaging for commercial containers of cenobamate must comply with **21 U.S.C. 825** and **958**(e), and be in accordance with **21 CFR part 1302**.

5. *Inventory.* Since March 10, 2020, every DEA registrant who possesses any quantity of cenobamate was required to keep an inventory of cenobamate on hand, pursuant to **21 U.S.C. 827** and **958**(e), and in accordance with **21 CFR 1304.03**, **1304.04**, and **1304.11**.

[[Page 51341]]

6. *Records and Reports.* DEA registrants must maintain records and submit reports for cenobamate, or products containing cenobamate, pursuant to **21 U.S.C. 827**, and **958**(e), and in accordance with **21 CFR parts 1304**, **1312**, and **1317**.

7. *Prescriptions.* All prescriptions for cenobamate, or products containing cenobamate, must comply with **21 U.S.C. 829**, and be issued in accordance with **21 CFR parts 1306** and **1311**, subpart C.

8. *Manufacturing and Distributing.* In addition to the general requirements of the CSA and DEA regulations that are applicable to manufacturers and distributors of schedule V controlled substances, such registrants should be advised that (consistent with the foregoing considerations) any manufacturing or distribution of cenobamate may only be for the legitimate purposes consistent with the drug's labeling, or for research activities authorized by the Federal Food, Drug, and Cosmetic Act and the CSA.

9. *Importation and Exportation.* All importation and exportation of cenobamate must be in compliance with **21 U.S.C. 952, 953, 957,** and **958**, and in accordance with **21 CFR part 1312.**

10. *Liability.* Any activity involving cenobamate not authorized by, or in violation of, the CSA or its implementing regulations, is unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

Regulatory Analyses

Administrative Procedure Act

This final rule, without change, affirms the amendment made by the interim final rule that is already in effect. Section 553 of the Administrative Procedure Act (APA) (5 U.S.C. 553) generally requires notice and comment for rulemaking. However, **21 U.S.C. 811**(j) provides that in cases where a certain new drug is: (1) Approved by HHS and (2) HHS recommends control in CSA schedule II-V, DEA shall issue an interim final rule scheduling the drug within 90 days. Additionally, subsection (j) specifies that the rulemaking shall become immediately effective as an interim final rule without requiring DEA to demonstrate good cause. DEA issued an interim final rule on March 10, 2020, and solicited public comments on that rule. Subsection (j) further provides that after giving interested persons the opportunity to comment and to request a hearing, the Attorney General, as delegated to the Administrator of DEA, shall issue a final rule in accordance with the scheduling criteria of 21 U.S.C. 811(b) through (d) and **812**(b). As stated above, the two public comments DEA received to the interim final rule did not necessitate any response. DEA is now issuing the final rule in accordance with subsection (j).

Executive Orders (E.O.) 12866, 13563, and 13771, Regulatory Planning and Review, Improving Regulation and Regulatory Review, and Reducing Regulation and Controlling Regulatory Costs

In accordance with **21 U.S.C. 811**(a) and (j), this scheduling action is subject to formal rulemaking procedures performed "on the record after opportunity for a hearing," which are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth the procedures and criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget (OMB) pursuant to section 3(d)(1) of E.O. 12866 and the principles reaffirmed in E.O. 13563.

This final rule is not an E.O. 13771 regulatory action pursuant to E.O. 12866 and OMB guidance.\1\

\1\ Office of Mgmt. & Budget, Exec. Office of The President, Interim Guidance Implementing Section 2 of the Executive Order of January 30, 2017 Titled "Reducing Regulating and Controlling Regulatory Costs" (Feb. 2, 2017).

E.O. 12988, Civil Justice Reform

This regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of E.O. 12988 to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

E.O. 13132, Federalism

This rulemaking does not have federalism implications warranting the application of E.O. 13132. The rule does not have substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government.

E.O. 13175, Consultation and Coordination With Indian Tribal Governments

This rule does not have tribal implications warranting the application of E.O. 13175. It does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal government and Indian tribes, or on the distribution of power and responsibilities between the Federal government and Indian tribes.

Regulatory Flexibility Act

The Regulatory Flexibility Act (RFA) (5 U.S.C. 601-612) applies to rules that are subject to notice and comment under section 553(b) of the APA. As noted in the above discussion regarding the applicability of the APA, DEA was not required to publish a general notice of proposed rulemaking. Consequently, the RFA does not apply.

Unfunded Mandates Reform Act of 1995

In accordance with the Unfunded Mandates Reform Act (UMRA) of 1995, 2 U.S.C. 1501 et seq., DEA has determined that this action would not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million or more (adjusted annually for inflation) in any 1 year." Therefore, neither a Small Government Agency Plan nor any other action is required under UMRA of 1995.

Paperwork Reduction Act of 1995

This action does not impose a new collection of information requirement under the Paperwork Reduction Act of 1995. 44 U.S.C. 3501-3521. This action does not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Congressional Review Act

This rule is not a major rule as defined by the Congressional Review Act (CRA), 5 U.S.C. 804. This rule will not result in: An annual effect on the economy of $100,000,000 or more; a major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; or significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of U.S.-based companies to compete with foreign-based companies in domestic and export markets. However, pursuant to the CRA, DEA has submitted a copy of this final rule to both Houses of Congress and to the Comptroller General.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

- Accordingly, the interim final rule amending **21 CFR part 1308**, which

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published on March 10, 2020 (**85 FR 13741**), is adopted as final without change.

Timothy J. Shea,
Acting Administrator.

[FR Doc. 2020-17357 Filed 8-19-20; 8:45 am]

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Rules - 2020

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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-558]

Schedules of Controlled Substances: Placement of Lasmiditan in Schedule V

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Interim final rule with request for comments.

SUMMARY: On October 11, 2019, the U.S. Food and Drug Administration approved a new drug application for Reyvow (lasmiditan) tablets for oral use. Lasmiditan is chemically known as [2,4,6-trifluoro-N-(6-(1-methylpiperidine-4-carbonyl)pyridine-2-yl-benzamide]. Thereafter, the Department of Health and Human Services provided the Drug Enforcement Administration (DEA) with a scheduling recommendation to place lasmiditan in schedule V of the Controlled Substances Act (CSA). In accordance with the CSA, as revised by the Improving Regulatory Transparency for New Medical Therapies Act, DEA is hereby issuing an interim final rule placing lasmiditan, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible, in schedule V of the CSA.

DATES: The effective date of this rulemaking is January 31, 2020. Interested persons may file written comments on this rulemaking in accordance with **21 U.S.C. 811**(j)(3) and **21 CFR 1308.43**(g). Electronic comments must be submitted, and written comments must be postmarked, on or before March 2, 2020. Commenters should be aware that the electronic Federal Docket Management System will not accept comments after 11:59 p.m. Eastern Time on the last day of the comment period.

Interested persons may file a request for hearing or waiver of hearing in accordance with **21 U.S.C. 811**(j)(3) and **21 CFR 1308.44**. Requests for hearing and waivers of an opportunity for a hearing or to participate in a hearing must be received on or before March 2, 2020.

ADDRESSES: To ensure proper handling of comments, please reference "Docket No. DEA-558" on all correspondence, including any attachments.

- *Electronic comments:* The Drug Enforcement Administration encourages that all comments be submitted electronically through the Federal eRulemaking Portal, which provides the ability to type short comments directly into the comment field on the web page or attach a file for lengthier comments. Please go to http://www.regulations.gov and follow the online instructions at that site for submitting comments. Upon completion of your submission, you will receive a Comment Tracking Number for your comment. Please be aware that submitted comments are not instantaneously available for public view on Regulations.gov. If you have received a Comment Tracking Number, your comment has been successfully submitted and there is no need to resubmit the same comment.
- *Paper comments:* Paper comments that duplicate the electronic submission are not necessary and are discouraged. Should you wish to mail a paper comment in lieu of an electronic comment, it should be sent via regular

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or express mail to: Drug Enforcement Administration, Attn: DEA Federal Register Representative/DRW, 8701 Morrissette Drive, Springfield, VA 22152.

- *Hearing requests:* All requests for hearing and waivers of participation must be sent to: Drug Enforcement Administration, Attn: Administrator, 8701 Morrissette Drive, Springfield, Virginia 22152. All requests for hearing and waivers of participation should also be sent to: (1) Drug Enforcement Administration, Attn: Hearing Clerk/LJ, 8701 Morrissette Drive, Springfield, Virginia 22152; and (2) Drug Enforcement Administration, Attn: DEA Federal Register Representative/DRW, 8701 Morrissette Drive, Springfield, Virginia 22152.

FOR FURTHER INFORMATION CONTACT: Scott A. Brinks, Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, VA 22152, Telephone: (571) 362-3261.

SUPPLEMENTARY INFORMATION:

Posting of Public Comments

Please note that all comments received are considered part of the public record. They will, unless reasonable cause is given, be made available by the Drug Enforcement Administration (DEA) for public inspection online at http://www.regulations.gov. Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter. The Freedom of Information Act (FOIA) applies to all comments received. If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want it to be made publicly available, you must include the phrase "PERSONAL IDENTIFYING INFORMATION" in the first paragraph of your comment. You must also place all of the personal identifying information you do not want made publicly available in the first paragraph of your comment and identify what information you want redacted.

If you want to submit confidential business information as part of your comment, but do not want it to be made publicly available, you must include the phrase "CONFIDENTIAL BUSINESS INFORMATION" in the first paragraph of your comment. You must also prominently identify the confidential business information to be redacted within the comment.

Comments containing personal identifying information and confidential business information identified as directed above will generally be made publicly available in redacted form. If a comment has so much confidential business information or personal identifying information that it cannot be effectively redacted, all or part of that comment may not be made publicly available. Comments posted to http://www.regulations.gov may include any personal identifying information (such as name, address, and phone number) included in the text of your electronic submission that is not identified as directed above as confidential.

An electronic copy of this document and supplemental information, including the complete Department of Health and Human Services and Drug Enforcement Administration eight-factor analyses, to this interim final rule are available at http://www.regulations.gov for easy reference.

Request for Hearing, or Waiver of Participation in Hearing

Pursuant to **21 U.S.C. 811**(a), this action is a formal rulemaking "on the record after opportunity for a hearing." Such proceedings are conducted pursuant to the provisions of the Administrative Procedure Act (APA), 5 U.S.C. 551-559. **21 CFR 1308.41-1308.45; 21 CFR part 1316**, subpart D. Interested persons may file requests for a hearing, or notices of intent to participate in a hearing, in conformity with the requirements of **21 CFR 1308.44**(a) or (b), and include a statement of interest in the proceeding and the objections or issues, if any, concerning which the person desires to be heard. Any interested person may file a waiver of an opportunity for a hearing or to participate in a hearing together with a written statement regarding the interested person's position on the matters of fact and law involved in any hearing as set forth in 21 CFR 1308.44(c).

All requests for a hearing and waivers of participation must be sent to DEA using the address information provided above.

Background and Legal Authority

Under the Improving Regulatory Transparency for New Medical Therapies Act (Pub. L. 114-89), which was signed into law on November 25, 2015, the DEA is required to commence an expedited scheduling action with respect to certain new drugs approved by the U.S. Food and Drug Administration (FDA). As provided in **21 U.S.C. 811**(j), this expedited scheduling is required where both of the following conditions apply: (1) The Secretary of the Department of Health and Human Services (Secretary of HHS or the Secretary) has advised DEA that a New Drug Application (NDA) has been submitted for a drug that has a stimulant, depressant, or hallucinogenic effect on the central nervous system (CNS), and that it appears that such drug has an abuse potential; and (2) the Secretary recommends that DEA control the drug in schedule II, III, IV, or V, pursuant to 21 U.S.C. 811(a) and (b). In these circumstances, DEA is required to issue an interim final rule controlling the drug within 90 days.

The law further states that the 90-day timeframe starts the later of: (1) The date DEA receives the HHS scientific and medical evaluation/scheduling recommendation, or (2) the date DEA receives notice of the NDA approval by HHS. In addition, the law specifies that the rulemaking shall become immediately effective as an interim final rule without requiring DEA to demonstrate good cause therefor. Thus, the purpose of subsection (j) is to speed the process by which DEA schedules newly approved drugs that are currently either in schedule I or not controlled (but which have sufficient abuse potential to warrant control) so that such drugs may be marketed without undue delay following FDA approval.\1\

\1\ Given the parameters of subsection (j), in DEA's view, it would not apply to a reformulation of a drug containing a substance currently in schedules II through V for which an NDA has recently been approved.

Subsection (j) further provides that the interim final rule shall give interested persons the opportunity to comment and to request a hearing. After the conclusion of such proceedings, DEA must issue a final rule in accordance with the scheduling criteria of subsections **21 U.S.C. 811**(b), (c), and (d) and **21 U.S.C. 812**(b).

Lasmiditan [2,4,6-trifluoro-N-(6-(1-methylpiperidine-4- carbonyl)pyridine-2-yl-benzamide] is a new molecular entity with central nervous system (CNS) depressant properties. Lasmiditan is a 5- hydroxytryptamine (5-HT, serotonin) 1F receptor agonist. One of its metabolites has low GABAA channel positive allosteric activity. On October 11, 2018, Eli Lilly and Company (Sponsor) submitted an NDA to FDA for Reyvow (lasmiditan) 50 and 100 mg oral tablets. On November 4, 2019, DEA received notification that FDA, on October 11, 2019, approved the NDA for Reyvow (lasmiditan), under section 505(c) of the FDCA, for the acute treatment of migraine with or without aura in adults.\2\

\2\ https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/211280Orig1s000ltr.pdf.

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Determination To Schedule Lasmiditan

On November 4, 2019, DEA received from HHS a scientific and medical evaluation document (dated October 23, 2019) prepared by the FDA related to lasmiditan. This document contained an eight-factor analysis of the abuse potential of lasmiditan, along with HHS' recommendation to control lasmiditan under schedule V of the CSA.

On December 4, 2019, the DEA requested clarification from HHS regarding supporting evidence for factors 6 and 7 listed in **21 U.S.C. 811**(c), as well as the third finding under **21 U.S.C. 812**(b)(5), for placement of lasmiditan in schedule V. HHS responded to the DEA via a letter on January 15, 2020, with the necessary clarification.

In response, DEA reviewed the scientific and medical evaluation and scheduling recommendation provided by HHS, along with all other relevant data, and completed its own eight-factor review document pursuant to **21 U.S.C. 811**(c). DEA concluded that lasmiditan met the **21 U.S.C. 812**(b)(5) criteria for placement in schedule V of the CSA.

Pursuant to **subsection 811**(j), and based on the HHS recommendation, NDA approval by HHS/FDA, and DEA's determination, DEA is issuing this interim final rule to schedule lasmiditan as a schedule V controlled substance under the CSA.

Included below is a brief summary of each factor as analyzed by HHS and DEA, and as considered by DEA in its scheduling action. Please note that both the DEA and HHS analyses are available in their entirety under "Supporting Documents" in the public docket for this interim final rule at http://www.regulations.gov, under Docket Number "DEA- 558." Full analysis of, and citations to, the information referenced in the summary may also be found in the supporting and related material.

1. *Its Actual or Relative Potential for Abuse:* As noted by HHS, lasmiditan is a new molecular entity that has not been marketed in the United States or any other country. As a result, information on the actual abuse of lasmiditan is limited. According to HHS, lasmiditan is not currently available for medical treatment, lasmiditan has not been diverted from legitimate sources, and individuals have not taken the substance in amounts sufficient to create a hazard to public health and safety. DEA further notes that there are no reports for lasmiditan in the National Forensic Laboratory Information System (NFLIS),\3\ which collects drug identification results from drug cases submitted to and analyzed by State and local forensic laboratories. There were also no reports in STARLIMS,\4\ DEA's laboratory drug evidence data system of record.

\3\ NFLIS is a national forensic laboratory reporting system that systematically collects results from drug chemistry analyses conducted by State and local forensic laboratories in the United States. NFLIS data were queried on 11/14/2019.

\4\ STARLIMS is a laboratory information management system that systematically collects results from drug chemistry analyses conducted by the DEA laboratories. On October 1, 2014, STARLIMS replaced STRIDE as the DEA laboratory drug evidence data system of record. STARLIMS data were queried on 11/18/2019.

Data from HHS outlined in Factors 2 and 3 demonstrate that lasmiditan is a 5-hydroxytryyptamine-1F (5-HT1F) receptor agonist. There are no 5-HT1F receptor agonists currently controlled in the CSA. Lasmiditan at the highest dose tested did produce reinforcing effects in a rat self-administration assay. Drug- liking visual analog scale (VAS) for lasmiditan were significantly higher than placebo and significantly lower than the schedule IV benzodiazepine alprazolam in an abuse potential study in humans (see Factor 3).

2. *Scientific Evidence of Its Pharmacological Effects, if Known:* According to HHS, lasmiditan functions as a 5-HT1F receptor agonist. HHS also further stated that lasmiditan does not bind to various other receptor targets (opioid, cannabinoid, GABAergic, or other ion channels) that are typically associated with abuse.

As shown by the studies summarized by HHS, lasmiditan did not produce abuse-related behaviors in the toxicity studies within mice, rats, and dogs. HHS stated that the studies demonstrating depressant effects such as weight loss, sedation, and hypothermia produced by lasmiditan could be due to its toxic concentrations of lasmiditan. In addition, results of the drug discrimination assay demonstrated that lasmiditan did not generalize to the discriminative stimulus effects of the benzodiazepine lorazepam (schedule IV); however, lasmiditan did produce reinforcing effects in the self-administration assay.

HHS described results from a Phase 1, randomized, double-blind, placebo-and active-controlled, crossover clinical trial in adult subjects who were recreational poly-drug users. The primary objective of this study was to assess the abuse potential of lasmiditan compared to alprazolam and placebo using the maximal effect score (Emax) of the at-the-moment 100-mm bipolar Drug Liking VAS.

Lasmiditan was evaluated by the comparison of Drug Liking Emax between each dose of lasmiditan and placebo. All doses of lasmiditan (100 mg, 200 mg, and 400 mg) produced significantly higher Emax than that of placebo indicating that lasmiditan has abuse potential. However, these effects of all doses of lasmiditan were significantly lower than alprazolam on mean Emax of Drug Liking.

Lasmiditan 200 mg (therapeutic dose), lasmiditan 400 mg (supratherapeutic dose), and alprazolam 2 mg (43-49 percent) produced euphoric mood to a similar extent. The lower dose of lasmiditan (100 mg) produced euphoric moods in 25 percent of subjects. Alprazolam produced a feeling of relaxation in more subjects than that produced by any dose of lasmiditan. According to HHS, this pattern of adverse events (AEs) suggests that lasmiditan has a similar or slightly less potential for abuse than alprazolam.

According to HHS, the Sponsor conducted eighteen Phase 1 studies in which AEs, including abuse-related AEs, were evaluated. In Phase 1, single-dose studies with healthy subjects, lasmiditan produced somnolence, feeling drunk, and euphoric mood. Euphoric mood occurred in five out of twelve studies for lasmiditan, and one out of seven studies for a control group. According to HHS, overall, the data from Phase 1 studies indicated that lasmiditan had more abuse-related AEs than placebo, and alprazolam showed a greater incidence of abuse-related AEs as compared to lasmiditan in one study.

HHS reviewed data from five Phase 2 and 3 studies and stated that, at therapeutic doses, lasmiditan displays abuse-related AEs to a greater extent than placebo. However, these AEs occur at a low frequency (about one percent).

3. *The State of Current Scientific Knowledge Regarding the Drug or Other Substance:* Appearing as a white to off-white solid, lasmiditan is highly soluble in water and freely soluble in methanol. Per HHS, none of the steps in the manufacturing process of lasmiditan produces or utilizes substances that have a known potential for abuse, nor can they be easily modified to generate a substance with abuse potential. A high level of expertise in and knowledge of organic chemistry is required to synthesize lasmiditan.

Rat studies demonstrate that lasmiditan has a half-life of approximately 31 hours. HHS also described lasmiditan pharmacokinetic data from another study conducted in beagle dogs in the fasted (overnight) state versus the fed state. The time measurement for maximal concentration

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(Tmax) was the only parameter that significantly differed between the fed (3.5 hours) and the fasted (1.25 hours) state, indicating that food has a significant slowing effect on the oral absorption of lasmiditan.

A separate study in male rats was conducted to compare the plasma and brain pharmacokinetic parameters, in addition to evaluating the bioavailability of lasmiditan. Results indicate that lasmiditan crosses the blood brain barrier and collects in the brain, producing exposure levels 2.5- to 3-fold higher than those in plasma. The Tmax in both plasma and brain was reached in 30 minutes. However, the maximum serum concentration was two- and three-fold higher in the brain as compared to plasma levels following oral and IV administration, respectively. The oral bioavailability of the drug was 63.3 percent.

As described by HHS, an in-vitro study was conducted to identify the human cytochrome P450 isozymes responsible for the in-vitro metabolism of lasmiditan. Results indicated the possible involvement of CYP1A2 in the production of metabolites M7, M8, and M18; CYP2D6 and CYP2C9 in the production of M7 and M18; and CYP2C19 and CYP3A4 in the production of M7 and M18.

4. *Its History and Current Pattern of Abuse:* Lasmiditan was approved by FDA on October 11, 2019. According to HHS, as a single active ingredient in a drug product formulation, lasmiditan has not been approved for therapeutic use in any other country. There is no information available relating to the history and current pattern of abuse of this formulation of lasmiditan or the active ingredient. As stated in Factor 1, DEA notes that there has been no diversion of lasmiditan based on NFLIS and STARLIMS data.

5. *The Scope, Duration, and Significance of Abuse:* As described in Factor 4, lasmiditan as a single entity has not been approved for therapeutic use outside of the United States. A search by DEA of the NFLIS and STARLIMS databases found no evidence of law enforcement encounters of lasmiditan in the United States. Based on the preclinical and clinical study data described by HHS (see Factor 2, above), and on available epidemiological data, the scope, duration, and significance of lasmiditan abuse would likely be lower than substances in schedule IV of the CSA and similar to that of a drug controlled in schedule V.

6. *What, if Any, Risk There Is to the Public Health:* As stated by HHS, the extent to which a drug has abuse potential is considered an indication of its public health risk. Based on the preclinical and clinical study data described by HHS (see Factor 2, above), lasmiditan has abuse potential and physical or psychological dependence (Factor 7) that is lower than substances in schedule IV of the CSA and similar to that of substances controlled in schedule V.

7. *Its Psychic or Physiological Dependence Liability:* HHS described an animal study that was conducted to assess the withdrawal effects of lasmiditan. Based on the data from the animal study, HHS concluded that lasmiditan does not produce signs consistent with physical dependence. HHS, in its clarification letter to DEA, stated that animal data, discussed in Factor 2, suggest that lasmiditan has the potential to produce psychological dependence less than that of substances in schedule IV and similar to that of substances in schedule V. HHS further added that these circumstances of uncertain physical dependence and limited psychological dependence have likewise been observed in their analyses of other schedule V drugs.

8. *Whether the Substance Is an Immediate Precursor of a Substance Already Controlled Under the CSA:* Lasmiditan is not an immediate precursor of a substance that is already controlled in the CSA as defined in **21 U.S.C. 802**(23).

Conclusion: After considering the scientific and medical evaluation conducted by HHS, HHS' recommendation, and DEA's own eight-factor analysis, DEA has determined that these facts and all relevant data constitute substantial evidence of a potential for abuse of lasmiditan. As such, DEA hereby schedules lasmiditan as a controlled substance under the CSA.

Determination of Appropriate Schedule

21 U.S.C. 812(b) requires the evaluation of a substance's abuse potential, accepted medical use, and safety for use under medical supervision for scheduling under the CSA as a controlled substance. After consideration of the above eight factors determinative of control of a substance (**21 U.S.C. 811**(c)), and a review of the scientific and medical evaluation and scheduling recommendation provided by HHS, DEA finds that lasmiditan meets the following criteria for placement in schedule V of the CSA pursuant to 21 U.S.C. 812(b)(5).

(1) Lasmiditan has a low potential for abuse relative to the drugs or other substances in Schedule IV.

As stated by HHS, lasmiditan, a 5-HT1F receptor agonist, did not bind to receptors typically associated with abuse (e.g., opioid, cannabinoid, GABAergic). In the drug discrimination paradigm, lasmiditan did not generalize to the discriminative stimulus effects of the benzodiazepine lorazepam. Lasmiditan did, however, produce reinforcing effects in the self-administration assay.

As detailed by HHS, in a human abuse-potential study, all doses of lasmiditan produced drug-liking scores that were significantly higher than that of placebo, indicating its abuse potential. Subjects following lasmiditan reported drug-liking scores that were significantly smaller than that of alprazolam (schedule IV drug), indicating that its abuse potential is less than that of alprazolam. Lasmiditan produced abuse-related adverse events to a greater extent than that of placebo, but with low frequency (about 1 percent).

(2) Lasmiditan has a currently accepted medical use in the United States.

The FDA recently approved the NDA for lasmiditan oral tablets for the acute treatment of migraine with or without aura in adults. Therefore, lasmiditan has a currently accepted medical use in treatment in the United States.

(3) Abuse of Lasmiditan may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule IV.

As stated by HHS, based on the totality of the available scientific data, lasmiditan may lead to physical or psychological dependence that is low relative to substances in schedule IV and similar to that of substances in schedule V.

Based on these findings, the Acting Administrator of DEA concludes that lasmiditan warrants control in schedule V of the CSA. **21 U.S.C. 812**(b)(5).

Requirements for Handling Lasmiditan

Lasmiditan is subject to the CSA's schedule V regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, reverse distribution, dispensing, importing, exporting, research, and conduct of instructional activities and chemical analysis with, and possession involving, schedule V substances, including the following:

1. *Registration.* Any person who handles (manufactures, distributes, reverse distributes, dispenses, imports, exports, engages in research, or conducts instructional activities or chemical analysis with, or possesses)

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lasmiditan, or who desires to handle lasmiditan, must be registered with the DEA to conduct such activities pursuant to **21 U.S.C. 822**, **823**, **957**, and **958**, and in accordance with **21 CFR parts 1301** and **1312**. Any person who currently handles or intends to handle lasmiditan, and is not registered with the DEA, must submit an application for registration and may not continue to handle lasmiditan, unless the DEA has approved that application for registration, pursuant to 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312.

2. *Disposal of Stocks.* Any person who does not desire, or is not able to obtain, a schedule V registration must surrender all quantities of currently held lasmiditan, or may transfer all quantities of currently held lasmiditan to a person registered with the DEA in accordance with **21 CFR part 1317**, in addition to all other applicable federal, state, local, and tribal laws.

3. *Security.* Lasmiditan is subject to schedule III-V security requirements and must be handled and stored in accordance with **21 CFR 1301.71-1301.93**.

4. *Labeling and Packaging.* All labels, labeling, and packaging for commercial containers of lasmiditan must comply with **21 U.S.C. 825** and **958**(e), and be in accordance with **21 CFR part 1302**.

5. *Inventory.* Every DEA registrant who possesses any quantity of lasmiditan must take an inventory of lasmiditan on hand, pursuant to **21 U.S.C. 827** and **958**(e), and in accordance with **21 CFR 1304.03**, **1304.04**, and **1304.11**.

Any person who becomes registered with the DEA to handle lasmiditan must take an initial inventory of all stocks of controlled substances (including lasmiditan) on hand on the date the registrant first engages in the handling of controlled substances, pursuant to **21 U.S.C. 827** and **958**(e), and in accordance with **21 CFR**

1304.03, 1304.04, and **1304.11.**

After the initial inventory, every DEA registrant must take a new inventory of all stocks of controlled substances (including lasmiditan) on hand every two years, pursuant to **21 U.S.C. 827** and **958(e),** and in accordance with **21 CFR 1304.03, 1304.04,** and **1304.11.**

6. *Records and Reports.* Every DEA registrant must maintain records and submit reports for lasmiditan, or products containing lasmiditan, pursuant to **21 U.S.C. 827** and **958(e),** and in accordance with **21 CFR parts 1304, 1312,** and **1317.**

7. *Prescriptions.* All prescriptions for lasmiditan, or products containing lasmiditan, must comply with **21 U.S.C. 829,** and be issued in accordance with **21 CFR parts 1306** and **1311,** subpart C.

8. *Manufacturing and Distributing.* In addition to the general requirements of the CSA and DEA regulations that are applicable to manufacturers and distributors of schedule V controlled substances, such registrants should be advised that (consistent with the foregoing considerations) any manufacturing or distribution of lasmiditan may only be for the legitimate purposes consistent with the drug's labeling, or for research activities authorized by the Federal Food, Drug, and Cosmetic Act and the CSA.

9. *Importation and Exportation.* All importation and exportation of lasmiditan must be in compliance with **21 U.S.C. 952, 953, 957,** and **958,** and in accordance with **21 CFR part 1312.**

10. *Liability.* Any activity involving lasmiditan not authorized by, or in violation of, the CSA or its implementing regulations, is unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

Regulatory Analyses

Administrative Procedure Act

Section 553 of the Administrative Procedure Act (APA) (5 U.S.C.) generally requires notice and comment for rulemakings. However, **21 U.S.C. 811** provides that in cases where a certain new drug is (1) approved by HHS and (2) HHS recommends control in CSA schedule II-V, DEA shall issue an interim final rule scheduling the drug within 90 days. Additionally, the law specifies that the rulemaking shall become immediately effective as an interim final rule without requiring DEA to demonstrate good cause.

Executive Orders 12866, 13563, and 13771, Regulatory Planning and Review, Improving Regulation and Regulatory Review, and Reducing Regulation and Controlling Regulatory Costs

In accordance with **21 U.S.C. 811**(a) and (j), this scheduling action is subject to formal rulemaking procedures performed "on the record after opportunity for a hearing," which are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth the procedures and criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget (OMB) pursuant to section 3(d)(1) of Executive Order 12866 and the principles reaffirmed in Executive Order 13563.

This final rule is not an Executive Order 13771 regulatory action pursuant to Executive Order 12866 and OMB guidance.\5\

\5\ Office of Mgmt. & Budget, Exec. Office of the President, Interim Guidance Implementing Section 2 of the Executive Order of January 30, 2017 Titled "Reducing Regulation and Controlling Regulatory Costs" (Feb. 2, 2017).

Executive Order 12988, Civil Justice Reform

This regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of Executive Order 12988 to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132, Federalism

This rulemaking does not have federalism implications warranting the application of Executive Order 13132. The rule does not have substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government.

Executive Order 13175, Consultation and Coordination With Indian Tribal Governments

This rule does not have tribal implications warranting the application of Executive Order 13175. It does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal government and Indian tribes, or on the distribution of power and responsibilities between the Federal government and Indian tribes.

Regulatory Flexibility Act

The Regulatory Flexibility Act (RFA) (5 U.S.C. 601-612) applies to rules that are subject to notice and comment under section 553(b) of the APA. Under **21 U.S.C. 811**(j), DEA is not required to publish a general notice of proposed rulemaking. Consequently, the RFA does not apply.

Unfunded Mandates Reform Act of 1995

In accordance with the Unfunded Mandates Reform Act (UMRA) of 1995, 2 U.S.C. 1501 et seq., DEA has determined that this action would not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any 1 year." Therefore, neither a Small Government Agency Plan nor any other action is required under UMRA of 1995.

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Paperwork Reduction Act of 1995

This action does not impose a new collection of information requirement under the Paperwork Reduction Act of 1995. 44 U.S.C. 3501- 3521. This action would not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Congressional Review Act

This rule is not a major rule as defined by the Congressional Review Act (CRA), 5 U.S.C. 804. This rule will not result in: An annual effect on the economy of $100,000,000 or more; a major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; or significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of U.S.-based companies to compete with foreign-based companies in domestic and export markets. However, pursuant to the CRA, DEA has submitted a copy of this interim final rule to both Houses of Congress and to the Comptroller General.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, DEA amends 21 CFR part 1308 as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

- 1. The authority citation for 21 CFR part 1308 continues to read as follows:

  Authority: 21 U.S.C. 811, 812, 871(b), unless otherwise noted.

- 2. Amend **Sec. 1308.15** by:
- a. Redesignating paragraph (e)(4) as (e)(5);
- b. Adding new paragraph (e)(4).

The addition reads as follows:

Sec. 1308.15 Schedule V.

* * * * *

(e) * * *

(4) Lasmiditan [2,4,6-trifluoro-*N*-(6-(1-methylpiperidine-4-carbonyl)pyridine-2-yl-benzamide]	2790

* * * * *

Dated: January 28, 2020.

Uttam Dhillon,
Acting Administrator.

[FR Doc. 2020-01957 Filed 1-30-20; 8:45 am]

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Rules - 2020

[Federal Register Volume 85, Number 163 (Friday, August 21, 2020)]
[Rules and Regulations]
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[FR Doc No: 2020-17356]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Parts 1308 **and 1312**

[Docket No. DEA-500]

RIN 1117-AB53

Implementation of the Agriculture Improvement Act of 2018

AGENCY: Drug Enforcement Administration (DEA), Department of Justice.

ACTION: Interim final rule with request for comments.

SUMMARY: The purpose of this interim final rule is to codify in the Drug Enforcement Administration (DEA) regulations the statutory amendments to the Controlled Substances Act (CSA) made by the Agriculture Improvement Act of 2018 (AIA), regarding the scope of regulatory controls over marihuana, tetrahydrocannabinols, and other marihuana-related constituents. This interim final rule merely conforms DEA's regulations to the statutory amendments to the CSA that have already taken effect, and it does not add additional requirements to the regulations.

DATES: Effective August 21, 2020. Electronic comments must be submitted, and written comments must be postmarked, on or before October 20, 2020. Commenters should be aware that the electronic Federal Docket Management System will not accept comments after 11:59 p.m. Eastern Time on the last day of the comment period.

ADDRESSES: To ensure proper handling of comments, please reference "RIN 1117-AB53/Docket No. DEA-500" on all correspondence, including any attachments.

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- *Electronic comments:* The Drug Enforcement Administration encourages that all comments be submitted electronically through the Federal eRulemaking Portal, which provides the ability to type short comments directly into the comment field on the web page or attach a file for lengthier comments. Please go to http://www.regulations.gov and follow the online instructions at that site for submitting comments. Upon completion of your submission, you will receive a Comment Tracking Number for your comment. Please be aware that submitted comments are not instantaneously available for public view on http://www.regulations.gov. If you have received a Comment Tracking Number, your comment has been successfully submitted, and there is no need to resubmit the same comment.
- *Paper comments:* Paper comments that duplicate the electronic submission are not necessary and are discouraged. Should you wish to mail a paper comment in lieu of an electronic comment, it should be sent via regular or express mail to: Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, Diversion Control Division; Mailing Address: 8701 Morrissette Drive, Springfield, VA 22152.

FOR FURTHER INFORMATION CONTACT: Scott A. Brinks, Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (202) 598-2596.

SUPPLEMENTARY INFORMATION:

Posting of Public Comments

Please note that all comments received are considered part of the public record. They will, unless reasonable cause is given, be made available by the Drug Enforcement Administration (DEA) for public inspection online at http://www.regulations.gov. Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter. The Freedom of Information Act (FOIA) applies to all comments received. If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want it to be made publicly available, you must include the phrase "PERSONAL IDENTIFYING INFORMATION" in the first paragraph of your comment. You must also place all of the personal identifying information you do not want made publicly available in the first paragraph of your comment and identify what information you want redacted.

If you want to submit confidential business information as part of your comment, but do not want it to be made publicly available, you must include the phrase "CONFIDENTIAL BUSINESS INFORMATION" in the first paragraph of your comment. You must also prominently identify the confidential business information to be redacted within the comment.

Comments containing personal identifying information and confidential business information identified as directed above will generally be made publicly available in redacted form. If a comment has so much confidential business information or personal identifying information that it cannot be effectively redacted, all or part of that comment may not be made publicly available. Comments posted to http://www.regulations.gov may include any personal identifying information (such as name, address, and phone number) included in the text of your electronic submission that is not identified as directed above as confidential.

An electronic copy of this document and the complete Economic Impact Analysis, to this interim final rule are available in their entirety under the tab "Supporting Documents" of the public docket of this action at http://www.regulations.gov under FDMS Docket ID: DEA-500 (RIN 1117-AB53/Docket Number DEA-500) for easy reference.

Executive Summary

The Agriculture Improvement Act of 2018, Public Law 115-334 (the AIA), was signed into law on December 20, 2018. It provided a new statutory definition of "hemp" and amended the definition of marihuana under **21 U.S.C. 802**(16) and the listing of tetrahydrocannabinols under 21 U.S.C. 812(c). The AIA thereby amends the regulatory controls over marihuana, tetrahydrocannabinols, and other marihuana-related constituents in the Controlled Substances Act (CSA).

This rulemaking makes four conforming changes to DEA's existing regulations:

- It modifies **21 CFR 1308.11**(d)(31) by adding language stating that the definition of "Tetrahydrocannabinols" does not include "any material, compound, mixture, or preparation that falls within the definition of hemp set forth in 7 U.S.C. 1639o."
- It removes from control in schedule V under **21 CFR 1308.15**(f) a "drug product in finished dosage formulation that has been approved by the U.S. Food and Drug Administration that contains cannabidiol (2-[1R-3-methyl-6R-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol) derived from cannabis and no more than 0.1% (w/w) residual tetrahydrocannabinols."
- It also removes the import and export controls described in **21 CFR 1312.30**(b) over those same substances.
- It modifies **21 CFR 1308.11**(d)(58) by stating that the definition of "Marihuana Extract" is limited to extracts "containing greater than 0.3 percent delta-9-tetrahydrocannabinol on a dry weight basis."

This interim final rule merely conforms DEA's regulations to the statutory amendments to the CSA that have already taken effect, and it does not add additional requirements to the regulations. Accordingly, there are no additional costs resulting from these regulatory changes. However, as discussed below, the changes reflected in this interim final rule are expected to result in annual cost savings for affected entities.

Changes to the Definition of Marihuana

The AIA amended the CSA's regulatory controls over marihuana by amending its definition under the CSA. Prior to the AIA, marihuana was defined in **21 U.S.C. 802**(16) as follows:

> The term "marihuana" means all parts of the plant Cannabis sativa L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin. Such term does not include the mature stalks of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination.

The AIA modified the foregoing definition by adding that the "term 'marihuana' does not include hemp, as defined in section 1639o of Title 7." **21 U.S.C. 802**(16)(B). Furthermore, the AIA added a definition of "hemp" to 7 U.S.C. 1639o, which reads as follows:

> The term 'hemp' means the plant Cannabis sativa L. and any part of that plant, including the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a delta-9-tetrahydrocannabinol concentration of not more than 0.3 percent on a dry weight basis.

Taken together, these two changes made by the AIA limit the definition of marihuana to only include cannabis or cannabis-derived material that contain more than 0.3% delta-9-tetrahydrocannabinol (also known as Δ^9-THC) on a dry weight basis. Thus, to fall within the current CSA definition of

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marihuana, cannabis and cannabis-derived material must both fall within the pre-AIA CSA definition of marihuana and contain more than 0.3 percent Δ^9-THC on a dry weight basis. Pursuant to the AIA, unless specifically controlled elsewhere under the CSA, any material previously controlled under Controlled Substance Code Number 7360 (marihuana) or under Controlled Substance Code Number 7350 (marihuana extract), that contains 0.3% or less of Δ^9-THC on a dry weight basis--i.e., "hemp" as that term defined under the AIA--is not controlled. Conversely, any such material that contains greater than 0.3% of Δ^9-THC on a dry weight basis remains controlled in schedule I.

In order to meet the AIA's definition of hemp, and thus qualify for the exception in the definition of marihuana, a cannabis-derived product must itself contain 0.3% or less Δ^9-THC on a dry weight basis. It is not enough that a product is labeled or advertised as "hemp." The U.S. Food and Drug Administration (FDA) has recently found that many cannabis-derived products do not contain the levels of cannabinoids that they claim to contain on their labels.\1\ Cannabis-derived products that exceed the 0.3% Δ^9-THC limit do not meet the statutory definition of "hemp" and are schedule I controlled substances, regardless of claims made to the contrary in the labeling or advertising of the products.

\1\ See FDA, Warning Letters and Test Results for Cannabidiol-Related Products, https://www.fda.gov/NewsEvents/PublicHealthFocus/ucm484109.htm.

In addition, the definition of hemp does not automatically exempt any product derived from a hemp plant, regardless of the Δ^9-THC content of the derivative. In order to meet the definition of "hemp," and thus qualify for the exemption from schedule I, the derivative must not exceed the 0.3% Δ^9-THC limit. The definition of "marihuana" continues to state that "all parts of the plant Cannabis sativa L.," and "every compound, manufacture, salt, derivative, mixture, or preparation of such plant," are schedule I controlled substances unless they meet the definition of "hemp" (by falling below the 0.3% Δ^9-THC limit on a dry weight basis) or are from exempt parts of the plant (such as mature stalks or non-germinating seeds). See **21 U.S.C. 802**(16) (emphasis added). As a result, a cannabis derivative, extract, or product that exceeds the 0.3% Δ^9-THC limit is a schedule I controlled substance, even if the plant from which it was derived contained 0.3% or less Δ^9-THC on a dry weight basis.

Finally, nothing in the AIA or in these implementing regulations affects or alters the requirements of the Food, Drug, & Cosmetic Act (FD&C Act). See 7 U.S.C. 1639r(c). Hemp products that fall within the jurisdiction of the FD&C Act must comply with its requirements. FDA has recently issued a statement regarding the agency's regulation of products containing cannabis and cannabis-derived compounds, and DEA refers interested parties to that statement, which can be found at https://www.fda.gov/newsevents/Newsroom/PressAnnouncements/ucm628988.htm.

Changes to the Definition of Tetrahydrocannabinols

The AIA also modified the listing for tetrahydrocannabinols under **21 U.S.C. 812**(c) by stating that the term tetrahydrocannabinols does not include tetrahydrocannabinols in hemp. Specifically, 21 U.S.C. 812(c) Schedule I now lists as schedule I controlled substances:

> "Tetrahydrocannabinols, except for tetrahydrocannabinols in hemp (as defined under section 1639o of Title 7)."

Therefore, the AIA limits the control of tetrahydrocannabinols (for Controlled Substance Code Number 7370). For tetrahydrocannabinols that are naturally occurring constituents of the plant material, Cannabis sativa L., any material that contains 0.3% or less of Δ^9-THC by dry weight is not controlled, unless specifically controlled elsewhere under the CSA. Conversely, for tetrahydrocannabinols that are naturally occurring constituents of Cannabis sativa L., any such material that contains greater than 0.3% of Δ^9-THC by dry weight remains a controlled substance in schedule I.

The AIA does not impact the control status of synthetically derived tetrahydrocannabinols (for Controlled Substance Code Number 7370) because the statutory definition of "hemp" is limited to materials that are derived from the plant Cannabis sativa L. For synthetically derived tetrahydrocannabinols, the concentration of Δ^9-THC is not a determining factor in whether the material is a controlled substance. All synthetically derived tetrahydrocannabinols remain schedule I controlled substances.

This rulemaking is modifying **21 CFR 1308.11**(d)(31) to reflect this statutory change. By this rulemaking, 21 CFR 1308.11(d)(31) is being modified via the addition of subsection (ii), which reads:

> "Tetrahydrocannabinols does not include any material, compound, mixture, or preparation that falls within the definition of hemp set forth in 7 U.S.C. 1639o."

Removal of Schedule V Control of FDA-Approved Products Containing Cannabidiol

Previously DEA, pursuant to **21 CFR 1308.15**, separately controlled in Schedule V drug products in finished dosage formulations that have been approved by FDA and that contain cannabidiol (CBD) derived from cannabis and no more than 0.1 percent (w/w) residual tetrahydrocannabinols (under Controlled Substance Code Number 7367). The FDA-approved substances described under Drug Code 7367 are no longer controlled, by virtue of the AIA. As a result, DEA is removing the listing for "Approved cannabidiol drugs" under schedule V in 21 CFR 1308.15.

Note that CBD in a mixture with a Δ^9-THC concentration greater than 0.3% by dry weight is not exempted from the definition of "marihuana" or "tetrahydrocannabinols." Accordingly, all such mixtures exceeding the 0.3% limit remain controlled substances under schedule I.

Removal of Import/Export Provisions Involving FDA-Approved Products Containing CBD

Previously DEA, pursuant to **21 CFR 1312.30**, required import and export permits pursuant to **21 U.S.C. 811**(d)(1), **952**(b)(2), and **953**(e)(3) for the import and export of drug products in finished dosage formulations that have been approved by FDA and that contain CBD derived from cannabis and no more than 0.1 percent (w/w) residual tetrahydrocannabinols. Because such substances are no longer controlled substances, DEA is likewise removing the import and export permit requirement for these substances. The regulation is revised to delete Sec. 1312.30(b).

Drug Code 7350 for Marihuana Extract

The current control status of marihuana-derived constituents depends upon the concentration of Δ^9-THC in the constituent. DEA is amending the scope of substances falling within the Controlled Substances Code Number for marihuana extract (7350) to conform to the amended definition of marihuana in the AIA. As amended, the Drug Code 7350 definition reads:

> Marihuana Extract--meaning an extract containing one or more cannabinoids that has been derived from any plant of the genus Cannabis, containing greater than 0.3 percent delta-9-tetrahydrocannabinol on a dry weight

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> basis, other than the separated resin (whether crude or purified) obtained from the plant.

21 CFR 1308.11(d)(58). The drug code 7350 became effective on January 13, 2017. 81 FR 90194.

Regulatory Analysis

Administrative Procedure Act

An agency may find good cause to exempt a rule from certain provisions of the Administrative Procedure Act (APA) (5 U.S.C. 553), including those requiring the publication of a prior notice of proposed rulemaking and the pre-promulgation opportunity for public comment, if such actions are determined to be unnecessary, impracticable, or contrary to the public interest.

DEA finds there is good cause within the meaning of the APA to issue these amendments as an interim final rule and to delay comment procedures to the post-publication period, because these amendments merely conform the implementing regulations to recent amendments to the CSA that have already taken effect. DEA has no discretion with respect to these amendments. This rule does no more than incorporate the statutory amendments into DEA's regulations, and publishing a notice of proposed rulemaking or soliciting public comment prior to publication is unnecessary. See 5 U.S.C. 553(b)(B) (relating to notice and comment procedures). "[W]hen regulations merely restate the statute they implement, notice-and-comment procedures are unnecessary." Gray Panthers Advocacy Committee v. Sullivan, 936 F.2d 1284, 1291 (D.C. Cir. 1991); see also United States v. Cain, 583 F.3d 408, 420 (6th Cir. 2009) (contrasting legislative rules, which require notice-and-comment procedures, "with regulations that merely restate or interpret statutory obligations," which do not); Komjathy v. Nat. Trans. Safety Bd., 832 F.2d 1294, 1296 (D.C. Cir. 1987) (when a rule "does no more than repeat, virtually verbatim, the statutory grant of authority" notice-and-comment procedures are not required).

In addition, because the statutory changes at issue have already been in effect since December 20, 2018, DEA finds good cause exists to make this rule effective immediately upon publication. See 5 U.S.C. 553(d). Therefore, DEA is issuing these amendments as an interim final rule, effective upon publication in the Federal Register.

Although publishing a notice of proposed rulemaking and soliciting public comment prior to publication are unnecessary in this instance because these regulations merely implement statutory changes over which the agency has no discretion, DEA is soliciting public comment on this rule following its publication. For that reason, DEA is publishing this rule as an interim final rule and is establishing a docket to receive public comment on this rule. To the extent required by law, DEA will consider and respond to any relevant comments received.

Executive Orders 12866 (Regulatory Planning and Review), 13563 (Improving Regulation and Regulatory Review), and 13771 (Reducing Regulation and Controlling Regulatory Cost)

This interim final rule was developed in accordance with the principles of Executive Orders (E.O.) 12866, 13563, and 13771. E.O. 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, if regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health, and safety effects; distributive impacts; and equity). E.O. 13563 is supplemental to and reaffirms the principles, structures, and definitions governing regulatory review as established in E.O. 12866. E.O. 12866 classifies a "significant regulatory action," requiring review by the Office of Management and Budget (OMB), as any regulatory action that is likely to result in a rule that may: (1) Have an annual effect on the economy of $100 million or more or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, or tribal governments or communities; (2) create a serious inconsistency or otherwise interfere with an action taken or planned by another agency; (3) materially alter the budgetary impact of entitlements, grants, user fees, or loan programs or the rights and obligations of recipients thereof; or (4) raise novel legal or policy issues arising out of legal mandates, the President's priorities, or the principles set forth in the E.O.

The economic, interagency, budgetary, legal, and policy implications of this interim final rule have been examined and it has been determined that it is not a significant regulatory action under E.O. 12866 because it is a non-discretionary action that is dictated by the statutory amendments to the CSA enacted by the AIA. While not determined to be a significant regulatory action, this action has been reviewed by the OMB.

As explained above, DEA is obligated to issue this interim final rule to revise its regulations so that they are consistent with the provisions of the CSA that were amended by the AIA. In issuing this interim final rule, DEA has not gone beyond the statutory text enacted by Congress. Thus, DEA would have to issue this interim final rule regardless of the outcome of the agency's regulatory analysis. Nonetheless, DEA conducted this analysis as discussed below.

Summary of Benefits and Costs

This analysis is limited to the provisions of the AIA that are being directly implemented by this DEA interim final rule. DEA has reviewed these regulatory changes and their expected costs and benefits. Benefits, in the form of cost savings realized by DEA registrants handling previously controlled substances, will be generated as a direct result of the publication of this interim final rule. DEA does not expect there to be any costs associated with the promulgation of this interim final rule. The following is a summary; a detailed economic analysis of the interim final rule can be found in the rulemaking docket at http://www.regulations.gov.

The AIA's revised definitions of marihuana and tetrahydrocannabinols effectively decontrol hemp as defined under the AIA. DEA's regulatory authority over any plant with less than 0.3% THC content on a dry weight basis, and any of the plant's derivatives under the 0.3% THC content limit, is removed as a result. It is important to note, however, that this does not mean that hemp is not under federal regulatory oversight. The AIA directs the U.S. Department of Agriculture (USDA) to review and approve commercial hemp production plans developed by State, territory, and Indian tribal agencies and to develop its own production plan. 7 U.S.C. 1639p, 1639q. Until these regulations are finalized, State commercial hemp pilot programs authorized under the 2014 Farm Bill are still in effect and current participants may proceed with plans to grow hemp while new regulations are drafted.\2\ DEA expects the USDA to assess the costs and benefits of this new regulatory apparatus once those rules are finalized. For these reasons, DEA considers any potential costs or benefits broadly related to changes in the domestic industrial hemp market due to the

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decontrol of hemp, including but not limited to the expansion in the number of producers, consumer products, and the impact on supply chains to be outside the scope of this analysis.

\2\ See USDA, Hemp Production Program Questions and Answers, https://www.ams.usda.gov/publications/content/hemp-production-program-questions-and-answers.

To determine any cost savings resulting from this decontrol action, DEA analyzed its registration, import, and export data. The removal of DEA's regulatory authority over hemp as defined under the AIA will impact only DEA registrants that currently import viable hemp seed intended for germination. Viable hemp seed was classified as a schedule I controlled substance prior to the amendments to the CSA enacted by the AIA. The importation and exportation of controlled substances requires an importer or exporter to first register with DEA, and then apply and obtain a permit to import or export controlled substances for each shipment.\3\ The decontrol of hemp with this interim final rule means that viable hemp seed is no longer subject to those schedule I requirements, as long as the material contains less than the 0.3% limit.

\3\ See **21 CFR 1312.11(a), 1312.21(a).**

Based on the number of import and export permits issued, DEA estimated the number of import and export permit applications that would no longer be needed. DEA reviewed internal data tracking the number of imports and exports for hemp seed over a three year period beginning January 1, 2016 and ending December 31, 2018.\4\ During this three year period, there was an average of 88 import permits issued for hemp seed per year, and no exports. These import permits were issued only to participants in state commercial hemp pilot programs, including state departments of agriculture and higher education institutions, which are considered "fee exempt", and do not pay the $1,523 annual importer registration fee.\5\ However, fee-exempt institutions are still required to obtain a DEA registration and renew that registration annually by filling out and submitting DEA form 225a. DEA expects these institutions to relinquish their schedule I importer registrations as a result of the promulgation of this interim final rule.

\4\ DEA import data is organized by drug code. Hemp seed falls within drug code "7360--Marihuana".

\5\ See **21 CFR 1301.21(a)(1).**

DEA estimates the average annual cost savings attributable to the elimination of import permits for hemp seed, and the elimination of annual registration renewals for hemp seed importers to be $3,225.\6\ This cost savings is realized entirely by DEA registrants. Since the anticipated reduction in import permits and registration

renewals being processed is negligible relative to the total amount of permits and renewals processed by DEA annually, DEA is not expected to experience a measurable decrease in workflow or use of resources, and therefore, will incur no cost savings. The results of this analysis are summarized below:

\6\ Rounded down to the nearest whole dollar.

Average Annual Import Permit Application (DEA Form 357) Cost Savings	
Estimated hourly wage ($/hour): \7\	$45.54
Load for benefits (percent of labor rate): \8\	*43%*
Loaded labor rate ($/hour): \9\	$65.06
Average hourly burden, per application:	0.25
Average annual # of import permit applications for hemp seed:	88
Average annual hemp seed import permit application labor costs: \10\	$1,431.32
Average annual mailing cost of hemp seed import permit applications: \11\	$1,579.50
Annual Registration Renewal Application (DEA Form 225a) Cost Savings	
Estimated hourly wage ($/hour): \12\	$59.56
Load for benefits (percent of labor rate): \13\	*43%*
Loaded labor rate ($/hour): \14\	$85.09
# of importers no longer requiring registration:	21
Average hourly burden, per application: \15\	0.12
Average annual registration renewal application labor cost: \16\	$214.43
Total Annual Cost Savings:	**$3,225.25**

This interim final rule removes FDA-approved products containing CBD from schedule V control, including controls over the importation and exportation of this class of drugs. There is currently only one drug that meets these criteria for decontrol.\17\ To determine any cost savings resulting from this decontrol action, DEA analyzed its registration, import, and export data. DEA believes all entities that currently handle FDA-approved CBD products also handle other controlled substances. This means the decontrol of this product will not allow these DEA registrants to benefit from any registration-related cost savings. However, like importers of viable hemp seed, importers and exporters of FDA-approved CBD products will no longer be required to obtain import and export permits from DEA.

\7\ Median hourly wage, Bureau of Labor Statistics, Occupational and Employment and Wages, May 2018, 11-3071 Transportation, Storage, and Distribution Managers (http://www.bls.gov/oes/current/oes_nat.htm). The DEA considers this occupational category to be representative of the type of employee that is likely to fill out and submit import permits on behalf of a DEA registered importer.

\8\ Bureau of Labor Statistics, "Employer Costs for Employee Compensation--March 2019" (ECEC) reports that average benefits for private industry is 30% of total compensation. The 30% of total compensation equates to 42.86% (30% / 70%) load on wages and salaries.

\9\ $45.54 x (1 + 0.4286) = $65.06.

\10\ ($65.06 x 0.25) x 88 = $1,431.32.

\11\ 91% of import permits are submitted via paper form and delivered to DEA by an express carrier with respondent-paid means for return delivery. The estimated cost burden is $19.50 per response: 2 x $9.75 = $19.50. $9.75 is based on a major express carrier's national 3-day flat rate for envelopes. The DEA assumes that 91% of import permits submitted in any given year incur this mailing cost.

\12\ Estimates are based on the population of the regulated industry participating in these business activities. The DEA assumes that a general and operations manager (11-1021, 2018 Standard Occupational Classification) will complete the form on behalf of the applicant or registrant.

\13\ Bureau of Labor Statistics, "Employer Costs for Employee Compensation--March 2019" (ECEC) reports that average benefits for private industry is 30% of total compensation. The 30% of total compensation equates to 42.86% (30% / 70%) load on wages and salaries.

\14\ $59.56 x (1 + 0.4286) = $85.09.

\15\ The DEA assumes all forms are submitted online.

\16\ ($85.09 x 0.5) x 21 = $214.43.

\17\ See FDA, Regulation of Cannabis and Cannabis-Derived Products: Questions and Answers, https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-questions-and-answers#approved.

DEA analyzed its internal import and export data to identify the average

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number of permits issued for FDA-approved CBD products over a three year period beginning January 1, 2016 and ending December 31, 2018. During this period there was an average of 52 import permits and one export permit issued per year, the elimination of which will result in an average annual cost savings of $1,814.\18\ This cost savings is realized entirely by DEA registrants. Since the anticipated reduction in import and export permits being processed is negligible relative to the total number of permits processed by DEA annually, DEA is not expected to experience a measurable decrease in workflow or use of resources, and therefore, will incur no cost savings. The results of this analysis are summarized below:

\18\ Rounded down to the nearest whole number.

Average Annual Import Permit Application (DEA Form 357) Cost Savings	
Estimated hourly wage ($/hour): \7\	$45.54
Load for benefits (percent of labor rate): \8\	*43%*
Loaded labor rate ($/hour): \9\	$65.06
Average hourly burden, per application:	0.25
Average annual # of import permit applications for FDA-approved CBD:	52
Average annual FDA-approved CBD import permit application labor costs: \19\	$845.74
Average annual mailing cost for import permit applications: \11\ \20\	$916.50
Average Annual Export Permit Application (DEA Form 161) Cost Savings	
Estimated hourly wage ($/hour): \7\	$45.54
Load for benefits (percent of labor rate): \8\	*43%*
Loaded labor rate ($/hour): \9\	$65.06
Average hourly burden, per collection:	0.5
Average annual # of export permit applications for FD-approved CBD:	1
Average annual FDA-approved CBD export permit application labor costs: \21\	$32.53
Average annual mailing cost of export permit applications: \11\	$19.50
Total Annual Cost Savings:	**$1,814.27**

This interim final rule amends the definition of marihuana extract to conform to the revised definitions of marihuana and tetrahydrocannabinols. This revised definition now includes the 0.3%-THC content limit for the extract, meaning hemp-derived extracts containing less than 0.3%-THC content are also decontrolled along with the plant itself. As discussed previously, the production of hemp and its extracts as defined under the AIA now falls under the same regulatory oversight shared between the States, territories, and Indian tribal agencies, and the USDA. The FDA also affirms its regulatory oversight over cannabis-derived compounds, such as CBD, whether or not these compounds are "classified as hemp under the 2018 Farm Bill." \22\ For these reasons, DEA considers any potential costs or benefits broadly related to changes in the markets for domestic hemp extracts due to their decontrol, including but not limited to the expansion in the number of producers, consumer products, and the impact on supply chains to be outside the scope of this analysis.

\19\ ($65.06 x 0.25) x 52 = $845.74.

\20\ 52 x .91 = 47 (rounded down) permits mailed per year; 47 x $19.50 = $916.50.

\21\ ($65.06 x 0.5) x 1 = $32.53.

\22\ Ibid.

Like FDA-approved CBD products and viable hemp seeds, entities no longer require a DEA registration or import and export permits to handle hemp extract that does not exceed the statutory 0.3% THC limit. DEA's import and export data does capture a minimal number of instances of the importation and exportation of CBD; however, this data does not detail whether or not the CBD was derived from Cannabis sativa L. plants containing less than 0.3% THC content. For this reason, DEA does not have a good basis to estimate the annual number of imported or exported hemp-derived extracts that no longer require permits as a result of the promulgation of this interim final rule, but after reviewing its data, believes this number to be minimal. Therefore, DEA concludes that this provision of the interim final rule is likely to result in a minimal benefit to DEA registrants, but DEA does not have a good basis to quantify this amount.

As part of its core function, DEA's Diversion Control Division is responsible for managing over 1.8 million DEA registrations, processing new and renewal registration applications, processing registration modification requests, issuing certificates of registration, issuing import and export permits, issuing renewal notifications, conducting due diligence, maintaining and operating supporting information systems, etc. Therefore, DEA does not anticipate it will realize any measurable cost savings to the government as a result of the negligible decreases in registrant services resulting from the promulgation of this interim final rule.

As described above, DEA estimates the average annual benefit in the form of cost savings to DEA registrants as a result of the promulgation of this interim final rule to be $5,039.\23\ DEA calculated the present value of this cost savings over a 20 year period at a 3 percent and 7 percent discount rate. At a 3 percent discount rate, the present value of benefits is $74,968, while the present value of costs is $0, making the net present value (NPV) $74,968. At a 7 percent discount rate, the present value of benefits is $53,383, the present value of costs is $0, making the NPV is $53,383.\24\ The table below summarizes the present value and annualized benefit calculations.

\23\ The total average annual cost savings resulting from the decontrol of viable hemp seed ($3,225) and FDA-approved CBD products ($1,814).

\24\ See Office of Mgmt. & Budget, Exec. Office of the President, OMB Circular A-4, Regulatory Analysis (2003).

Present Value and Annualized Benefit Calculations		
Discount Rate	3%	7%
Annual benefit ($)	5,039	5,039
Present value of benefits ($)	74,968	53,383
Present value of costs ($)	0	0
Years	20	20
Net present value ($)	74,968	53,383

Figures are rounded.

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E.O. 13771 deregulatory actions are final actions that have totals costs less than zero. Also, under E.O. 13771, regulatory actions that expand production options, which are considered to be "enabling rules," generally qualify as E.O. 13771 deregulatory actions. This interim final rule decontrols hemp, hemp extracts and FDA-approved products containing CBD, and it results in cost savings to the public, as discussed above. Accordingly, DEA has determined that this interim final rule is an E.O. 13771 Deregulatory Action.

Executive Order 12988

This interim final rule meets the applicable standards set forth in sections 3(a) and 3(b)(2) of E.O. 12988, Civil Justice Reform, to eliminate ambiguity, minimize litigation, establish clear legal standards, and reduce burdens.

Executive Order 13132

This rulemaking does not preempt or modify any provision of State law, impose enforcement responsibilities on any State, or diminish the power of any State to enforce its own laws. Accordingly, this rulemaking does not have federalism implications warranting the application of E.O. 13132.

Executive Order 13175

This interim final rule is required by statute, and will not have tribal implications or impose substantial direct compliance costs on Indian tribal governments.

Regulatory Flexibility Act

The Regulatory Flexibility Act (RFA) applies to rules that are subject to notice and comment under section 553(b) of the Administrative Procedure Act (5 U.S.C. 553). As explained in the interim final rule, DEA determined that there was good cause to exempt this interim final rule from pre-publication notice and comment. Consequently, the RFA does not apply to this interim final rule.

Paperwork Reduction Act of 1995

This interim final rule does not involve a collection of information within the meaning of the Paperwork Reduction Act of 1995, 44 U.S.C. 3501-21.

Unfunded Mandates Reform Act of 1995

This interim final rule will not result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $136,000,000 or more (adjusted for inflation) in any one year, and will not significantly or uniquely affect small governments. Therefore, no actions were deemed necessary under the provisions of the Unfunded Mandates Reform Act of 1995. 2 U.S.C. 1532.

Congressional Review Act

This interim final rule is not a major rule as defined by the Congressional Review Act (CRA) (5 U.S.C. 804). DEA is submitting the required reports with a copy of this interim final rule to both Houses of Congress and to the Comptroller General.

List of Subjects

21 CFR Part 1308

Administrative practice and procedure; Drug traffic control; Reporting and recordkeeping requirements.

21 CFR Part 1312

Administrative practice and procedure; Drug traffic control; Exports; Imports; Reporting and recordkeeping requirements.

For the reasons set forth above, 21 CFR parts 1308 and 1312 are amended as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

- 1. The authority citation for part 1308 continues to read as follows:

  Authority: 21 U.S.C. 811, 812, 871(b), 956(b).

- 2. In **Sec. 1308.11**, paragraphs (d)(31) and (58) are revised to read as follows:

Sec. 1308.11 Schedule I.

* * * * *

(d) * * *

(31) Tetrahydrocannabinols	7370
(i) Meaning tetrahydrocannabinols, except as in paragraph (d)(31)(ii) of this section, naturally contained in a plant of the genus Cannabis (cannabis plant), as well as synthetic equivalents of the substances contained in the cannabis plant, or in the resinous extractives of such plant, and/or synthetic substances, derivatives, and their isomers with similar chemical structure and pharmacological activity to those substances contained in the plant, such as the following:	
1 cis or trans tetrahydrocannabinol, and their optical isomers	

6 cis or trans tetrahydrocannabinol, and their optical isomers
3, 4 cis or trans tetrahydrocannabinol, and its optical isomers
(Since nomenclature of these substances is not internationally standardized, compounds of these structures, regardless of numerical designation of atomic positions covered.)
(ii) Tetrahydrocannabinols does not include any material, compound, mixture, or preparation that falls within the definition of hemp set forth in 7 U.S.C. 1639o.

* * * * *

(58) Marihuana Extract	7350
Meaning an extract containing one or more cannabinoids that has been derived from any plant of the genus Cannabis, containing greater than 0.3% delta-9-tetrahydrocannabinol on a dry weight basis, other than the separated resin (whether crude or purified) obtained from the plant.	

* * * * *

Sec. 1308.15 [Amended]

- 3. In **Sec. 1308.15**, paragraph (f) is removed.

PART 1312--IMPORTATION AND EXPORTATION OF CONTROLLED SUBSTANCES

- 4. The authority citation for part 1312 continues to read as follows:

  Authority: 21 U.S.C. 821, 871(b), **952, 953, 954, 957, 958.**

Sec. 1312.30 [Amended]

- 5. In **Sec. 1312.30**, paragraph (b) is removed and reserved.

Timothy J. Shea,
Acting Administrator.

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