State of North Dakota
Doug Burgum, Governor

OFFICE OF THE EXECUTIVE DIRECTOR
1906 E Broadway Ave
Bismarck ND 58501-4700
Telephone (701) 328-9535
Fax (701) 328-9536
STATE BOARD OF PHARMACY
Email= Mhardy@ndboard.pharmacy
www.ndboard.pharmacy

Mark J. Hardy, PharmD
Executive Director

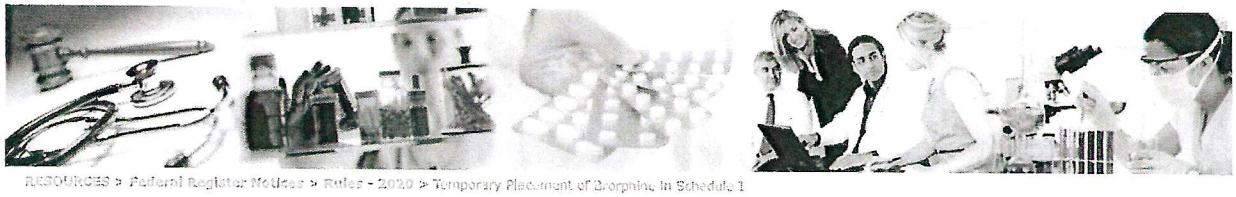
SB2059 Proposed Amendments.

1. Page 2, add under line 17 (and renumber accordingly): k. Brorphine
2. Page 8, line 7: Strike ~~title 4.1~~ and replace with chapter 4.1-18.1
3. Page 12, line 5: Remove the extra parenthesis at the end of: AKB48 N-(4-FLUOROBENZYL)~~)~~.
4. Page 13, line 11: Extra parenthesis at the end of: Other names: 5F-CUMYL-PINACA, SGT-25~~)~~.
5. Page 19, lines 5 & 6: Strike language:
   ~~(mm) 1-(4-methoxyphenyl)-N-methylpropan-2-amine (also known as paramethoxymethamphetamine and PMMA).~~
6. Page 23, add under line 6:
   (k) 1-(4-methoxyphenyl)-N-methylpropan-2-amine (also known as paramethoxymethamphetamine and PMMA).
7. Page 23, line 22 & 23: add "Samidorphan" to exclusion;
   nalbuphine, naldemedine, nalmefene, naloxegol, naloxone, 6 beta-naltrexol, ~~and~~ naltrexone, and samidorphan and their respective salts, but including the following:
8. Page 27, line 2: Add highlighted compound and separate out to subsections
   c. Immediate precursors to fentanyl: ~~4-anilino-N-phenethyl-4-piperidine (ANPP).~~
      (1) 4-anilino-N-phenethylpiperidine (ANPP).
      (2) *N*-phenyl-*N*-(piperidin-4-yl)propionamide (norfentanyl).

Potential amendment to bring clarity to the definition of "Marijuana" under Page 1 Lines 1-18

"Marijuana"

a. Means all parts of the plant cannabis sativa L., whether growing or not; the seeds thereof; the resin extracted from any part of the plant; and every compound, manufacture, salt, derivative, mixture, or preparation of the plant, its seeds, or resin.
b. Does not include:
   1. The mature stalks of the plant, fiber produced from the stalks, oil or cake made from the seeds of the plant, any other compound, manufacture, salt, derivative, mixture, or preparation of mature stalks (except the resin extracted therefrom), fiber, oil, or cake, or the sterilized seed of the plant which is incapable of germination,
   2. Hemp as defined in chapter 4.1-18.1 or
   3. A prescription drug approved by the United States food and drug administration under section 505 of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 355].



[Federal Register Volume 85, Number 233 (Thursday, December 3, 2020)]
[Proposed Rules]
[Pages 78047-78050]
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[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.

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 95 (Friday, May 15, 2020)]
[Proposed Rules]
[Pages 29359-29366]
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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.

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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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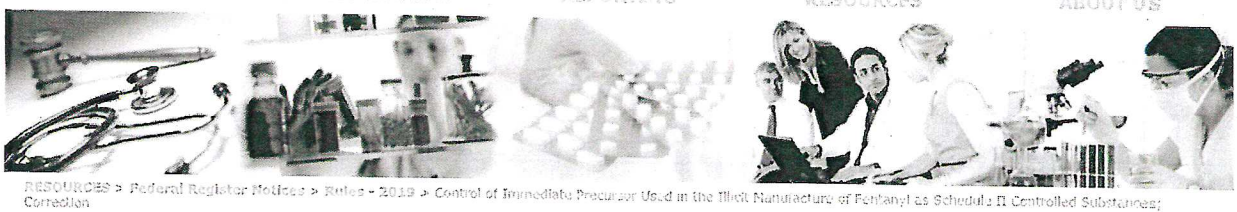

[Federal Register Volume 84, Number 26 (Thursday, February 7, 2019)]
[Rules and Regulations]
[Pages 2448-2449]
From the Federal Register Online via the Government Publishing Office [www.gpo.gov]
[FR Doc No: 2019-01470]

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

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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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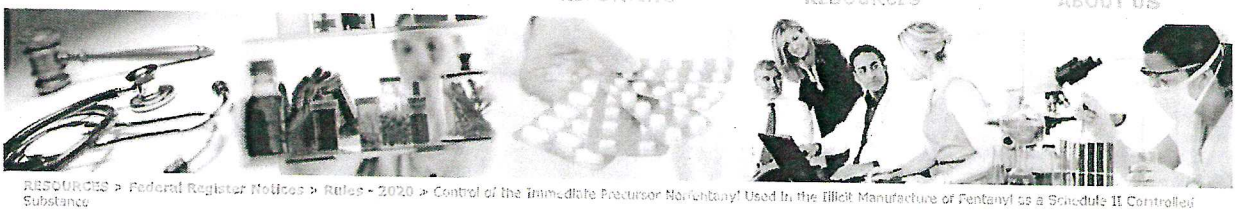

[Federal Register Volume 85, Number 75 (Friday, April 17, 2020)]
[Rules and Regulations]
[Pages 21320-21325]
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[FR Doc No: 2020-07381]

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.

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