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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].

The identification of buprenorphine on the illicit drug market has been reported in the United States, Canada, Belgium, and Sweden. Data obtained from preclinical pharmacology studies show that buprenorphine 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 buprenorphine and other potent opioids, the use of buprenorphine 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 buprenorphine has been associated with at least seven fatalities between June 2020 and July 2020 in the United States. Thus, buprenorphine poses an imminent hazard to public safety.

Available data and information for buprenorphine, 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

Buprenorphine is part of a structural class of compounds known as substituted piperidine benzimidazolones. The general synthesis of buprenorphine was first reported in the literature in 2018. Buprenorphine 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 buprenorphine in the United States; hence, there is no legitimate channel for buprenorphine as a marketed drug product. The appearance of buprenorphine 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, buprenorphine emerged in the U.S. illicit, synthetic drug market as evidenced by buprenorphine's identification in drug seizures. Between July and September of 2019, buprenorphine was first reported in drug casework in Canada and was first reported in police seizures in Sweden in March 2020.¹³

¹³ 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.

Buprenorphine has been encountered by U.S. law enforcement in powder form. In the United States, buprenorphine has been identified as a single substance and in combination with other substances. Twenty reports of buprenorphine have been reported in the National Forensic Laboratory Information System (NFLIS) in 2019 and 2020 from three different states (see Factor 5).¹⁴ In several NFLIS encounters, buprenorphine 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 buprenorphine in combination with fluprazolam, a non-scheduled benzodiazepine, and diphenhydramine, an over-the-counter antihistamine.¹⁵

¹⁴ 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.

¹⁵ 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) Laboratory¹⁶ in June and July 2020 verified the appearance of buprenorphine. Buprenorphine 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, buprenorphine was found in combination with fentanyl, fluprazolam, and heroin. Evidence suggests that individuals are using buprenorphine as a replacement to heroin or other opioids, either knowingly or unknowingly.

¹⁶ 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

Buprenorphine 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, buprenorphine 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 fluprazolam, a non-scheduled 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 buprenorphine from Ohio (4), Pennsylvania (1), and Wisconsin (15) in 2019 and 2020. NFLIS was queried on August 18, 2020, for buprenorphine. Due to the rapid appearance of the drug, buprenorphine 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 buprenorphine 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 buprenorphine seizures and post-mortem toxicology reports. Because abusers of buprenorphine are likely to obtain it through unregulated sources, the identity, purity, and quantity of buprenorphine 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),¹⁷ 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 buprenorphine. Individuals who initiate use (i.e., use a drug for the first time) of buprenorphine 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 buprenorphine is being illicitly distributed and abused.

¹⁷ 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 buprenorphine exhibits a pharmacological profile similar to that of other mu ([micro])-opioid receptor agonists. Data from in vitro studies completed in 2020 showed that buprenorphine binds to and activates the [micro]-opioid receptors. In the [35S]GTP[gamma]S cell-based receptor assay, buprenorphine, similar to fentanyl, acted as a [micro]-opioid receptor agonist. Buprenorphine'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. Buprenorphine 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 buprenorphine 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 buprenorphine into the illicit market may serve as a portal to problematic opioid use for those seeking these powerful opioids.

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:



RESOURCES > Federal Register Notices > Rules - 2020 > Placement of para-Methoxymethamphetamine (PMMA) in Schedule I

Rules - 2020

[Federal Register Volume 85, Number 95 (Friday, May 15, 2020)]

[Proposed Rules]

[Pages 29359-29366]

From the Federal Register Online via the Government Publishing Office [www.gpo.gov]

[FR Doc No: 2020-09599]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-509]

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

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Notice of proposed rulemaking.

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

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

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

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

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

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

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-methoxyphenylacetone, 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 Addiction (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 reposit 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.

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 aged ranges 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.

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) * * *

[[Page 29366]]

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

Uttam Dhillon,
Acting Administrator.

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

BILLING CODE 4410-09-P

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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)(1), 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).

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.A.N. 4566, 4603.

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.

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).

receive brain stimulation.¹⁸ 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.

¹⁸ 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 T_{max} 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 [³⁵S]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.

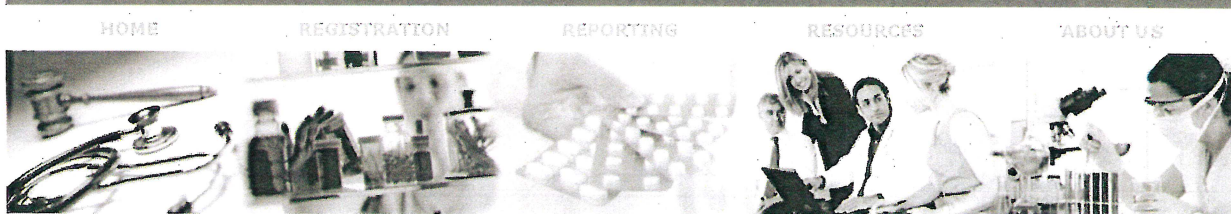
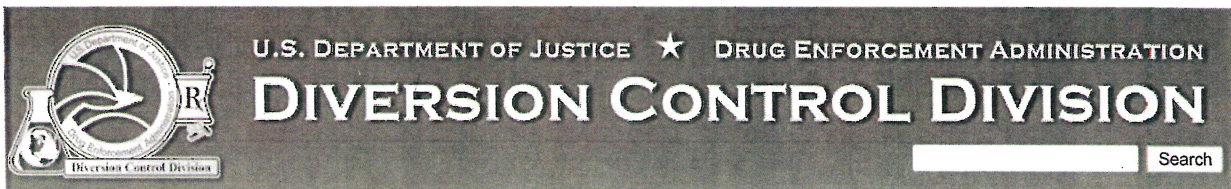
Samidorphan is not considered an immediate precursor of any controlled substance listed under the CSA as defined by **21 U.S.C. 802(23)**.

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



RESOURCES > Federal Register Notices > Rules - 2019 > Control of Immediate Precursor Used in the Illicit Manufacture of Fentanyl as Schedule II Controlled Substances; Correction

Rules - 2019

[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 Morrisette 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\

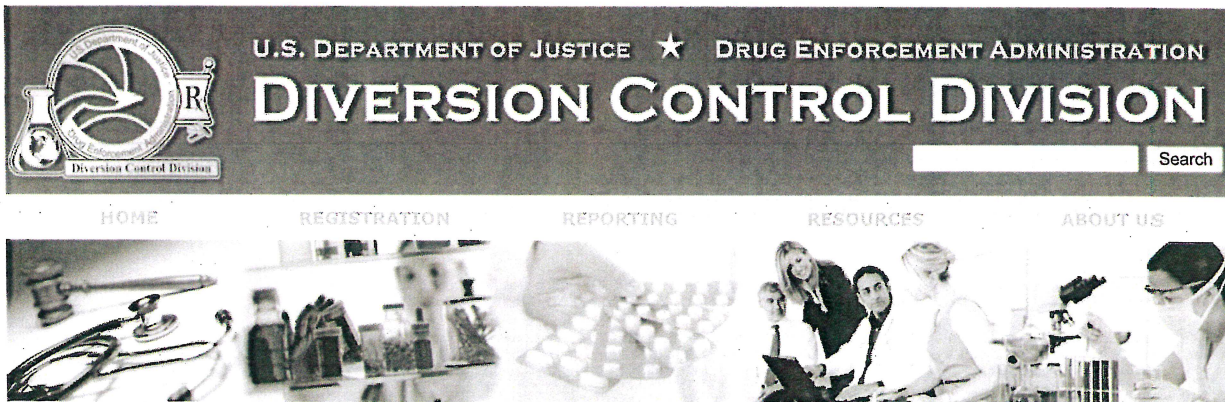
\2\ 5 U.S.C. 553(b)(B).

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.



RESOURCES > Federal Register Notices > Rules - 2020 > Control of the Immediate Precursor Norfentanyl Used in the Illicit Manufacture of Fentanyl as a Schedule II Controlled Substance

Rules - 2020

[Federal Register Volume 85, Number 75 (Friday, April 17, 2020)]
 [Rules and Regulations]
 [Pages 21320-21325]
 From the Federal Register Online via the Government Publishing Office [www.gpo.gov]
 [FR Doc No: 2020-07381]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-496]

Control of the Immediate Precursor Norfentanyl Used in the Illicit Manufacture of Fentanyl as a Schedule II Controlled Substance

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final rule.

SUMMARY: The Drug Enforcement Administration (DEA) is designating the precursor chemical, N-phenyl-N-(piperidin-4-yl)propionamide (norfentanyl) as an immediate precursor for the schedule II controlled substance fentanyl. Furthermore, DEA is finalizing the control of norfentanyl as a schedule II substance under the Controlled Substances Act (CSA).

DATES: This rulemaking becomes effective May 18, 2020.

FOR FURTHER INFORMATION CONTACT: Scott A. Brinks, Regulatory Drafting and Policy Support Section (DPW), Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrisette 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, Karisa 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.

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.

(g) ***

(3) ***

(ii) *N*-phenyl-*N*-(piperidin-4-yl)propionamide (norfentanyl)

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Dated: March 5, 2020.

Uttam Dhillon,
Acting Administrator.

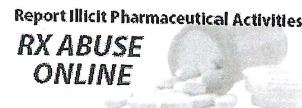
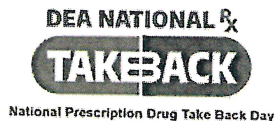
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