The Proposed Amendment

In consideration of the foregoing, the Federal Aviation Administration proposes to amend 14 CFR part 71 as follows:

PART 71—DESIGNATION OF CLASS A, B, C, D, AND E AIRSPACE AREAS; AIR TRAFFIC SERVICE ROUTES; AND REPORTING POINTS

■ 1. The authority citation for part 71 continues to read as follows:

Authority: 49 U.S.C. 106(f), 106(g); 40103, 40113, 40120; E.O. 10854, 24 FR 9565, 3 CFR, 1959–1963 Comp., p. 389.

§ 71.1 [Amended]

■ 2. The incorporation by reference in 14 CFR 71.1 of FAA Order 7400.11E, Airspace Designations and Reporting Points, dated July 21, 2020 and effective September 15, 2020, is amended as follows:

Paragraph 2066 United States Area Navigation Routes.

* * * * *

Q–437 VILLS, NJ to SLANG, VT [New]		
VILLS, NJ	FIX	(Lat. 39°18′03.87″ N, long. 075°06′37.89″ W)
DITCH, NJ	FIX	(Lat. 39°47′37.86″ N, long. 074°42′59.88″ W)
LUIGI, NJ	FIX	(Lat. 40°04′09.65″ N, long. 074°26′40.32″ W)
HNNAH, NJ	FIX	(Lat. 40°28′12.73″ N, long. 074°02′36.62″ W)
LLUND, NY	FIX	(Lat. 40°51′45.04″ N, long. 073°46′57.30″ W)
BIZEX, NY	WP	(Lat. 41°17′02.86″ N, long. 073°34′50.20″ W)
BINGS, NY	WP	(Lat. 42°00′33.26″ N, long. 073°30′01.81″ W)
WARUV, NY	FIX	(Lat. 42°45′52.14″ N, long. 073°34′41.41″ W)
SLANG, VT	WP	(Lat. 43°14′24.64″ N, long. 073°11′09.69″ W)

* * * * *

Issued in Washington, DC, on December 2, 2020.

George Gonzalez,

Acting Manager, Rules and Regulations Group.

[FR Doc. 2020–26947 Filed 12–9–20; 8:45 am]

BILLING CODE 4910–13–P

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

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.

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.

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. 21

[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.

[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).

[3] 28 CFR 0.100(b).

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.

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]

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.

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 [^{35}S]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 C_{max} = 4320 ng/mL, T_{max} = 1.2 hr, half-life = 4.1 hr, and AUC_{last} = 30,500 hr•ng/mL. In regard to cardiac activity, the female and male groups produced a slight decrease in

[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.

[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.

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 $GABA_A$ 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 ED_{50} 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

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.

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 E_{max} of Drug Liking VAS scores of 76.1 and 82, respectively and these were significantly higher than the placebo. The E_{max} 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 $C_{21}H_{26}N_2O_4$ 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 [^{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

[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).

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]

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

[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).

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 § 1308.12, revise the introductory text of paragraph (b)(1) to read as follows:

§ 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]

BILLING CODE 4410–09–P

DEPARTMENT OF TRANSPORTATION

National Highway Traffic Safety Administration

49 CFR Part 571

[Docket No. NHTSA–2020–0109]

RIN 2127–AM04

Federal Motor Vehicle Safety Standards: Test Procedures

AGENCY: National Highway Traffic Safety Administration (NHTSA), Department of Transportation (DOT).

ACTION: Advance notice of proposed rulemaking (ANPRM).

SUMMARY: NHTSA is issuing this ANPRM to seek public comment on whether any test procedures for any Federal Motor Vehicle Safety Standards (FMVSS) may be a candidate for replacement, repeal, or modification, for reasons other than for considerations relevant only to automated driving systems (ADS). This document is a continuation of the Agency's efforts to improve the FMVSS and minimize burdens. The Agency takes this action in response to its review of the FMVSS and to public comments solicited by DOT in a 2017 notice on its regulatory reform efforts. The commenters requested that NHTSA amend test procedures for air brakes and occupant crash protection. NHTSA has also identified some possible additional test procedure issues and discusses them in this Notice. In addition, this ANPRM also seeks comments and supporting information relating to any other test procedures which may be a candidate for replacement, repeal or modification, not just those specifically discussed in this Notice.

DATES: Comments must be received no later than February 8, 2021. See the Public Participation heading of the **SUPPLEMENTARY INFORMATION** section of this document for more information about written comments.

ADDRESSES: You may submit comments to the docket number identified in the heading of this document by any of the following methods:

- *Federal eRulemaking Portal:* Go to *http://www.regulations.gov.* Follow the online instructions for submitting comments.
- *Mail:* Docket Management Facility: U.S. Department of Transportation, 1200 New Jersey Avenue SE, West Building Ground Floor, Room W12–140, Washington, DC 20590–0001
- *Hand Delivery or Courier:* 1200 New Jersey Avenue SE, West Building Ground Floor, Room W12–140, between 9 a.m. and 5 p.m. ET, Monday through Friday, except Federal holidays.
- *Fax:* 202–493–2251.

Instructions: For detailed instructions on submitting comments and additional information on the rulemaking process, see the Public Participation heading of the **SUPPLEMENTARY INFORMATION** section of this document. Note that all comments received will be posted without change to *http://www.regulations.gov,* including any personal information provided. Please see the ''Privacy Act'' heading below.

Privacy Act: Anyone is able to search the electronic form of all comments received into any docket by the name of the individual submitting the comment (or signing the comment, if submitted on behalf of an association, business, labor union, etc.). You may review