



Billing Code 4410-09-P

**DEPARTMENT OF JUSTICE**

**Drug Enforcement Administration**

**21 CFR Part 1308**

**[Docket No. DEA-468]**

**Schedules of Controlled Substances: Removal of Naldemedine from Control**

**AGENCY:** Drug Enforcement Administration, Department of Justice.

**ACTION:** Notice of proposed rulemaking.

**SUMMARY:** The Drug Enforcement Administration (DEA) proposes to remove naldemedine (4*R*,4*aS*,7*aR*,12*bS*)-3-(cyclopropylmethyl)-4*a*,7,9-trihydroxy-*N*-(2-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl)-2,3,4,4*a*,5,7*a*-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-6-carboxamide) including its salts from the schedules of the Controlled Substances Act (CSA). This action is pursuant to the CSA which requires that such actions be made on the record after opportunity for a hearing through formal rulemaking. Naldemedine 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 naldemedine.

**DATES:** Interested persons may file written comments on this proposal in accordance with 21 CFR 1308.43(g). Comments must be submitted electronically or postmarked on

or before [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER]. Commenters should be aware that the electronic Federal Docket Management System will not accept comments after 11:59 p.m. Eastern Time on the last day of the comment period.

Interested persons, may file a request for hearing or waiver of hearing pursuant to 21 CFR 1308.44 and in accordance with 21 CFR 1316.45, 1316.47, 1316.48, and/or 1316.49, 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 [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER].

**ADDRESSES:** To ensure proper handling of comments, please reference “Docket No. DEA-468” on all electronic and written correspondence, including any attachments.

- *Electronic comments:* The Drug Enforcement Administration encourages that all comments be submitted electronically through the Federal eRulemaking Portal which provides the ability to type short comments directly into the comment field on the web page or attach a file for lengthier comments. Please go to <http://www.regulations.gov> and follow the online instructions at that site for submitting comments. Upon completion of your submission you will receive a Comment Tracking Number for your comment. Please be aware that submitted comments are not instantaneously available for public view on Regulations.gov. If you have received a Comment Tracking Number, your comment has been successfully submitted and there is no need to resubmit the same comment.

- *Paper comments:* Paper comments that duplicate the electronic submission are not necessary. 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 a 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: (1) Drug Enforcement Administration, Attn: Hearing Clerk/LJ, 8701 Morrisette Drive, Springfield, Virginia 22152; and (2) Drug Enforcement Administration, Attn: DEA Federal Register Representative/DRW, 8701 Morrisette Drive, Springfield, Virginia 22152.

**FOR FURTHER INFORMATION CONTACT:** Michael J. Lewis, Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrisette Drive, Springfield, Virginia 22152; Telephone: (202) 598-6812.

**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 (FOIA) applies to all comments received. If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want it to be made publicly available, you must include the phrase

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

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

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

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

### **Request for Hearing, or Waiver of Participation in Hearing**

Pursuant to 21 U.S.C. 811(a), this action is a formal rulemaking “on the record after opportunity for a hearing.” Such proceedings are conducted pursuant to the provisions of the Administrative Procedure Act (APA), 5 U.S.C. 551–559. 21 CFR 1308.41–1308.45; 21 CFR part 1316, subpart D. 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 only by interested persons, defined as those “adversely affected or aggrieved by any rule or proposed rule issuable pursuant to section 201 of the Act (21 U.S.C. 811).” 21 CFR 1300.01. Such requests or notices must conform to the requirements of 21 CFR 1308.44(a) or (b), and in accordance with 21 CFR 1316.45, 1316.47, 1316.48, and/or 1316.49 as applicable, and include a statement of 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 may include 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), the purpose and subject matter of a hearing held in relation to this rulemaking is restricted to: “(A) find[ing] that such drug or other substance has a potential for abuse, and (B) mak[ing] with respect to such drug or other substance the findings prescribed by subsection (b) of section 812 of this title for the schedule in which such drug is to be placed \* \* \*.” All requests for hearing and waivers of participation must be sent to the DEA using the address information provided above.

### **Legal Authority**

Pursuant to 21 U.S.C. 811(a)(2), the Attorney General may, by rule, “remove any drug or other substance from the schedules if he finds that the drug or other substance does not meet the requirements for inclusion in any schedule.” The Attorney General has delegated scheduling authority under 21 U.S.C. 811 to the Administrator of the DEA. 28 CFR 0.100.

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)<sup>1</sup>, or (3) on the petition of any interested party. 21 U.S.C. 811(a). This action was initiated at the request of the Acting Assistant Secretary for Health of the HHS and by a petition by the sponsor to DEA to remove naldemedine from the list of scheduled controlled substances of the CSA, and is supported by, *inter alia*, a recommendation from the Assistant Secretary of the HHS and an evaluation of all relevant data by the DEA. 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 naldemedine.

## **Background**

Naldemedine, known chemically as (4*R*,4*aS*,7*aR*,12*bS*)-3-(cyclopropylmethyl)-4*a*,7,9-trihydroxy-*N*-(2-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl)-2,3,4,4*a*,5,7*a*-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-6-carboxamide, is an opium alkaloid derivative. Naldemedine is a high-affinity antagonist at the mu, kappa, and delta opioid receptors. On March 23, 2016, a new drug application (NDA) was submitted by Shionogi (Sponsor) to the Food and Drug Administration (FDA) for approval of

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

naldemedine for the treatment of opioid induced constipation in patients with chronic non-cancer pain.

On June 8, 2016, the DEA received a petition from the drug sponsor (Shionogi, Inc.), requesting that the DEA amend 21 CFR 1308.12(b)(1) to exclude naldemedine as a schedule II substance from the Controlled Substances Act (CSA). The petitioner stated that naldemedine is a potent peripherally acting mu-opioid receptor antagonist. In accordance with 21 CFR 1308.43(c), the DEA accepted the petition for filing on August 5, 2016.

On March 23, 2017, the FDA approved naldemedine for marketing under the trade name Symproic® (0.2 mg tablets)<sup>2</sup>. Naldemedine is indicated for the treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain. Opioid-induced constipation is caused by an activation of mu-opioid receptors in the gastrointestinal tract. Naldemedine, a peripheral acting mu-opioid antagonist, can prevent OIC.

Naldemedine is a schedule II controlled substance under 21 U.S.C. §812(a)(1) and 21 C.F.R. §1308.12(b)(I), as a derivative of opium alkaloids and opiates.

### **Proposed Determination to Decontrol Naldemedine**

According to the HHS, the sponsor submitted a New Drug Application (NDA) for naldemedine on March 23, 2016. In the NDA submission, the sponsor requested that naldemedine and its salts be removed from all schedules for control under the CSA. Based on the NDA, the HHS mentioned that naldemedine is an antagonist of peripheral opioid receptors.

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<sup>2</sup> [http://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2017/208854Orig1s000ltr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2017/208854Orig1s000ltr.pdf) (last accessed 04/13/2017).

On March 22, 2017, the HHS provided the DEA with a scientific and medical evaluation document prepared by the FDA entitled “Basis for the Recommendation to Decontrol Naldemedine and its Salts from the Controlled Substances Act.” Pursuant to 21 U.S.C. 811(b), this document contained an eight-factor analysis of the abuse potential of naldemedine as a new drug, along with the HHS’ recommendation to decontrol naldemedine from the schedules of the CSA.

In response, the DEA reviewed the scientific and medical evaluations and scheduling recommendation provided by the HHS, and all other relevant data, and completed its own eight-factor review document on naldemedine pursuant to 21 U.S.C. 811(c). Included below is a brief summary of each factor as analyzed by the HHS and DEA, and as considered by the DEA in this proposal to remove naldemedine from the schedules of the CSA. Please note that both the 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-468.

1. *The Drug’s Actual or Relative Potential for Abuse.*

Naldemedine is a high affinity peripherally acting mu-opioid receptor antagonist. According to HHS, naldemedine is not available or marketed in any country, so there is a lack of evidence of diversion, illicit manufacturing, or deliberate ingestion (HHS review, 2017). Data obtained from scientific behavioral studies (drug discrimination and self-administration) show that naldemedine does not demonstrate a potential for abuse (HHS review, 2017). In clinical studies, naldemedine did not produce euphoria or abuse potential related adverse events (AEs) (HHS review, 2017). These data demonstrate that naldemedine lacks a potential for abuse.

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

Data submitted by HHS demonstrate that naldemedine binds strongly to all three opioid receptor sites: mu, kappa and delta, and acts as an antagonist at all three opioid receptor sites. Under both acute and chronic administration of naldemedine, penetration into the blood-brain barrier was non-significant, thereby suggesting that naldemedine is unlikely to have abuse potential (HHS review, 2017). Data obtained from *in vivo* studies conducted by Kanemasa (2015)<sup>3</sup> demonstrate that naldemedine potently inhibits constipating effects produced by opioids and that pretreatment with naldemedine (up to 30 mg/kg) had no influence on morphine's analgesic effect in rats.

According to the HHS, results obtained from Phase 1 study conducted in a single-dose pooled population (n = 224) showed that naldemedine was well tolerated in healthy subjects not taking opioid medications (HHS review, 2017). HHS also presented adverse events (AEs) from three pooled phase 3 repeated dose studies with naldemedine (n = 1,163 vs placebo, n = 1,165). It was noted by HHS that naldemedine was well tolerated in individuals taking opioid drugs. AEs reported at a rate  $\geq 2\%$  for naldemedine included nasopharyngitis, upper respiratory tract infection, urinary tract infection, diarrhea, abdominal distention, abdominal pain, flatulence, nausea, vomiting, hyperhidrosis, arthralgia, and back pain. Headache was the only centrally-mediated AE reported (2%) for individuals taking naldemedine, but it should be noted that individuals in the placebo group also reported headaches at the same percentage (2%). There were no reports of

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<sup>3</sup> Kanemasa T, Koike K, Arai T, Horita N, Chiba H, Tsuyoshi K, Hasegawa M. 2015. Effects of Naldemedine: A Peripherally Acting Mu-Opioid Receptor Antagonist in Rat Models of Opioid-Induced Constipation. *American Journal of Gastroenterology*. S110: 1322.

euphoria, hallucination or other abuse-related adverse events in either the naldemedine or placebo-treated groups.

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

Naldemedine tosylate (active ingredient in naldemedine drug product) is known chemically as (4*R*,4*aS*,7*aR*,12*bS*)-3-(cyclopropylmethyl)-4*a*,7,9-trihydroxy-*N*-(2-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-yl)-2,3,4,4*a*,5,7*a*-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-6-carboxamide 4-methylbenzenesulfonate.

According to HHS, naldemedine tosylate is slightly soluble in water and ethanol, soluble in methanol, and freely soluble in dimethylsulfoxide. Naldemedine tosylate is synthesized in a two-step/four-reaction derivation process from naltrexone hydrochloride, an opioid antagonist. The HHS further notes that the side chain addition makes naldemedine's lipid solubility low and thereby reduces its ability to cross the blood-brain barrier.

HHS reported that the Sponsor studied the pharmacokinetic profile of naldemedine in humans. Study participants were administered a single oral dose of naldemedine (0.1 – 100 mg). Data endpoints that were studied included time to peak plasma concentrations (T<sub>max</sub>), peak plasma concentrations (C<sub>max</sub>), area under the curve (AUC), and drug half-life (t<sub>1/2</sub>). Over the tested doses (0.1 – 100 mg naldemedine), the pharmacokinetic parameter ranges were as follows: T<sub>max</sub> – 0.5 to 1.0 hours; C<sub>max</sub> – 2 ng/ml to 2560 ng/ml; AUC – 11 ng.h/ml to 3980 ng.h/ml; t<sub>1/2</sub> - ~9 hours for all doses.

### 4. *Its History and Current Pattern of Abuse.*

Naldemedine is not marketed in the United States or in other countries. Based on its pharmacological similarities to other opioid receptor antagonists, naltrexone, naloxone

and naloxegol, it is unlikely that naldemedine possesses abuse related indications.

According to the HHS, there has been no evidence of abuse-related symptoms associated with naldemedine from the preclinical and clinical studies.

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

The DEA searched the National Forensic Laboratory Information System (NFLIS)<sup>4</sup> and STARLiMS (a web-based, commercial laboratory information management system)<sup>5</sup> databases; there have been no reports of naldemedine seizures in the United States. As mentioned in Factors 1 and 2, there were no abuse or euphoria-related adverse events reported from naldemedine use in clinical trials submitted by the Sponsor in the NDA submission.

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

According to the HHS, there are no signs or symptoms that show that naldemedine has abuse potential; hence, the possibility of abuse and public health risk is very unlikely. Naldemedine at a dose up to 5-times the recommended dose did result in cardiotoxicity (Migoya et al 2017)<sup>6</sup>. Naldemedine's mechanism of action as a mu-opioid receptor antagonist and lack of cardiotoxicity underscores its minimal potential to be associated with public health risk and public health risk as related to abuse.

*7. Its Psychic or Physiological Dependence Liability.*

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<sup>4</sup> NFLIS is a national drug forensic laboratory reporting system that systematically collects results from drug chemistry analyses conducted by participating Federal, State and local forensic laboratories across the country.

<sup>5</sup> STRIDE was a database of drug exhibits sent to DEA laboratories for analysis. STRIDE collected the results of drug evidence analyzed at DEA laboratories and reflects evidence submitted by the DEA, other Federal law enforcement agencies, and some local law enforcement agencies. On October 1, 2014, STARLiMS replaced STRIDE as the DEA laboratory drug evidence data system of record. DEA laboratory data submitted after September 30, 2014 are repositied in STARLiMS.

<sup>6</sup> Migoya E, Fukumura K, Yamada T, Arjona Ferreira J. 2017. Effect of naldemedine, a peripherally acting mu-opioidreceptor antagonist, on QT interval. *The Journal of Pain* S81:426.

In *in vivo* physical dependence studies, both during the drug administration period and 7 days following drug discontinuation, no symptoms of physical dependence were observed for naldemedine (HHS review, 2017). The HHS also mentioned that the lack of naldemedine self-administration by animals is consistent with a lack of psychic dependence liability. Hence, naldemedine does not have psychological or physical dependence liability.

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

Naldemedine is not considered an immediate precursor of any controlled substance.

**Conclusion**

Based on the recommendation of the Assistant Secretary for Health, received in accordance with section 201(b) of the Act (21 U.S.C. § 811(b)), and the independent review of the available data by DEA, the Acting Administrator of DEA, pursuant to sections 201(a) and 201(b) of the Act (21 U.S.C. §§ 811(a) and 811(c)), finds that:

- (1) Naldemedine has no potential for abuse and does not meet the finding for control under any CSA schedule. Naldemedine is a high-affinity antagonist at the three opioid receptors, mu, delta, and kappa. It is not related in action to a drug or other substance already listed as having potential for abuse and has no abuse potential.
- (2) Naldemedine has a currently accepted medical use in the United States;  
Naldemedine was approved for marketing on March 23, 2017 under the brand name Symproic® for the treatment of opioid-induced constipation in adults with chronic non-cancer pain.

(3) Naldemedine does not have physical or psychological dependence potential;

Naldemedine does not produce physical dependence in animals. In animal self-administration studies, naldemedine did not produce significant self-administration infusions. Hence, naldemedine does not have psychological dependence liability.

Based on these findings, the Acting Administrator of DEA concludes that naldemedine does not meet the requirements for inclusion in any schedule, and should be removed from control under the CSA.

### **Regulatory Analyses**

#### *Executive Orders 12866 and 15363*

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 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.

#### *Executive Order 12988*

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

#### *Executive Order 13132*

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*

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 Administrator, in accordance with the Regulatory Flexibility Act (5 U.S.C. 601-612) (RFA), has reviewed this proposed rule and by approving it certifies that it will not, if promulgated, have a significant economic impact on a substantial number of small entities. The purpose of this rule is to remove naldemedine 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 naldemedine. 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, naldemedine. Due to the wide variety of unidentifiable and unquantifiable variables that potentially could influence handling of naldemedine, the DEA is unable to determine the number of entities and small entities which would handle naldemedine.

However, the DEA estimates that all persons who would handle, or propose to handle naldemedine, are currently registered with the DEA to handle controlled substances. Therefore, the 1.7 million (1,683,023 as of April 2016) controlled substance registrations, representing approximately 436,761 entities, would be the maximum number of entities affected by this rule. The DEA estimates that 425,856 (97.5%) of 436,761 affected entities are “small entities” in accordance with the RFA and Small Business Administration size standards.

The DEA estimates all controlled substances registrants handle both controlled and non-controlled substances and these registrants are expected to continue to handle naldemedine if the proposed rule were finalized. Additionally, since prospective naldemedine handlers are likely to handle other controlled substances, the cost benefits they would receive as a result of the de-control of naldemedine is minimal. As naldemedine handlers continue to handle other controlled substances, they will need to maintain their DEA registration and keep the same security and recordkeeping processes, equipment, and facilities in place and would experience only minimal reduction in security, inventory, recordkeeping, and labeling costs. Physical security control requirements are the same for controlled substances listed in schedules II, III, IV, and V for the vast majority of registrants (practitioners).

While the DEA does not have a basis to estimate the number of affected entities, the DEA estimates that the maximum number of affected entities is 436,761 of which 425,856 are estimated to be small entities. Since the affected entities are expected to handle other controlled substances and maintain security and recordkeeping facilities and processes consistent with controlled substances, the DEA estimates any economic impact

will be minimal. Because of these facts, this rule will not, if promulgated, have a significant economic impact on a substantial number of small entities.

*Unfunded Mandates Reform Act of 1995*

In accordance with the Unfunded Mandates Reform Act (UMRA) of 1995, 2 U.S.C. 1501 *et seq.*, the DEA has determined and certifies that this action would not result in any Federal mandate that may result “in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted for inflation) in any one year \* \* \*.” Therefore, neither a Small Government Agency Plan nor any other action is required under UMRA of 1995.

*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. 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, the DEA proposes to amend 21 CFR part 1308:

**PART 1308— SCHEDULES OF CONTROLLED SUBSTANCES**

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

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

2. In § 1308.12, amend 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, and naltrexone, and their respective salts, but including the following:

\* \* \* \* \*

Dated: July 5, 2017

Chuck Rosenberg,  
*Acting Administrator.*

[FR Doc. 2017-14482 Filed: 7/11/2017 8:45 am; Publication Date: 7/12/2017]