contacting Ms. Regina Washington at (202) 586–1214 or by email: *Regina.Washington@ee.doe.gov* so that the necessary procedures can be completed.

DOE requires visitors to have laptops and other devices, such as tablets, checked upon entry into the building. Any person wishing to bring these devices into the Forrestal Building will be required to obtain a property pass. Visitors should avoid bringing these devices, or allow an extra 45 minutes to check in. Please report to the visitor's desk to have devices checked before proceeding through security.

Due to the REAL ID Act implemented by the Department of Homeland Security (''DHS''), there have been recent changes regarding ID requirements for individuals wishing to enter Federal buildings from specific states and U.S. territories. DHS maintains an updated website identifying the State and territory driver's licenses that currently are acceptable for entry into DOE facilities at *https://www.dhs.gov/real-id-enforcement-brief.* Acceptable alternate forms of Photo-ID include a U.S. Passport or Passport Card; an Enhanced Driver's License or Enhanced ID-Card issued by States and territories identified on the DHS website (Enhanced licenses issued by these states are clearly marked Enhanced or Enhanced Driver's License); a military ID; or other Federal government issued Photo-ID card.

B. Procedure for Submitting Prepared General Statements for Distribution

Any person who has plans to present a prepared general statement may request that copies of his or her statement be made available at the public meeting. Such persons may submit requests, along with an advance electronic copy of their statement in PDF (preferred), Microsoft Word or Excel, WordPerfect, or text (ASCII) file format, to the appropriate address shown in the **ADDRESSES** section at the beginning of this document. The request and advance copy of statements must be received at least one week before the public meeting and may be emailed, hand-delivered, or sent by mail. DOE prefers to receive requests and advance copies via email. Please include a telephone number to enable DOE staff to make a follow-up contact, if needed.

C. Conduct of Public Meeting

DOE will designate a DOE official to preside at the public meeting and may also use a professional facilitator to aid discussion. The meeting will not be a judicial or evidentiary-type public hearing, but DOE will conduct it in accordance with section 336 of EPCA (42 U.S.C. 6306). A court reporter will be present to record the proceedings and prepare a transcript. DOE reserves the right to schedule the order of presentations and to establish the procedures governing the conduct of the public meeting. After the public meeting and until the end of the comment period, interested parties may submit further comments on the proceedings and any aspect of the rulemaking.

The public meeting will be conducted in an informal, conference style. DOE will present summaries of comments received before the public meeting, allow time for prepared general statements by participants, and encourage all interested parties to share their views on issues affecting this rulemaking. Each participant will be allowed to make a general statement (within time limits determined by DOE), before the discussion of specific topics. DOE will permit, as time permits, other participants to comment briefly on any general statements.

At the end of all prepared statements on a topic, DOE will permit participants to clarify their statements briefly and comment on statements made by others. Participants should be prepared to answer questions by DOE and by other participants concerning these issues. DOE representatives may also ask questions of participants concerning other matters relevant to this rulemaking. The official conducting the public meeting will accept additional comments or questions from those attending, as time permits. The presiding official will announce any further procedural rules or modification of the above procedures that may be needed for the proper conduct of the public meeting.

A transcript of the public meeting will be included in the docket, which can be viewed as described in the Docket section at the beginning of this document. In addition, any person may buy a copy of the transcript from the transcribing reporter.

Signed in Washington, DC, on August 13, 2019.

Alexander N. Fitzsimmons,

Acting Deputy Assistant Secretary for Energy Efficiency, Energy Efficiency and Renewable Energy.

[FR Doc. 2019–17894 Filed 8–20–19; 8:45 am]

BILLING CODE 6450–01–P

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA–492]

Schedules of Controlled Substances: Removal of 6β-naltrexol From Control

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Drug Enforcement Administration (DEA) proposes to remove (5α,6β)-17-(cyclopropylmethyl)-4,5-epoxymorphinan-3,6,14-triol (6β-naltrexol) 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. 6β-Naltrexol 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 6β-naltrexol.

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 September 20, 2019. 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, defined at 21 CFR 1300.01 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),'' 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 September 20, 2019.

ADDRESSES: To ensure proper handling of comments, please reference ''Docket No. DEA–492'' on all correspondence, including any attachments.

• *Electronic comments:* The 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/ODXL, 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/LJ, 8701 Morrissette Drive, Springfield, Virginia 22152.

FOR FURTHER INFORMATION CONTACT: Scott A. Brinks, Regulatory Drafting and Policy Support Section, Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (202) 598–8106.

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 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 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. The DEA specifically solicits written comments regarding the DEA's economic analysis of the impact of these proposed changes. The 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 (APA) (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) through (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 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), the purpose and subject matter of a hearing 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 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 two petitions to remove 6β-naltrexol 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. 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 6β-naltrexol.

Background

6β-Naltrexol is the major metabolite of naltrexone. Naltrexone and 6β-naltrexol are reversible opioid receptor antagonists. Opioid receptor antagonists are commonly used in the treatment of

[1] As discussed in a memorandum of understanding entered into by the Food and Drug Administration (FDA) and the National Institute on Drug Abuse (NIDA), the FDA acts as the lead agency within 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.

opioid addiction and overdose. On December 24, 1974, naloxone, an opioid receptor antagonist that works similarly to naltrexone, was removed from all schedules for control under the CSA. Effective on March 6, 1975, Title 21 of the Code of Federal Regulations was amended to remove naltrexone from all schedules for control under the CSA. The Administrator of the DEA found that both naltrexone and naloxone and their salts have an accepted medical use for treatment in the United States and that they do not have a potential for abuse to justify continued control in any schedule under the CSA. In June 2003 and April 2008, the DEA received two separate citizen petitions to initiate proceedings to amend 21 CFR 1308.12(b)(1) so as to decontrol 6β-naltrexol from schedule II of the CSA. These petitions complied with the requirements of 21 CFR 1308.44(b) and were accepted for filing. Both petitioners argue that 6β-naltrexol has been characterized as an opioid receptor antagonist, a class of drugs with no abuse potential.

Proposed Determination To Decontrol 6β-Naltrexol

Pursuant to 21 U.S.C. 811(b), the DEA gathered the necessary data on 6β-naltrexol and forwarded the data, the sponsors' petitions, and a request for scheduling recommendation on 6β-naltrexol to the Department of Health and Human Services (HHS) on August 11, 2009. On July 21, 2017, the HHS provided to the DEA a scientific and medical evaluation entitled ''Basis For The Recommendation To Remove (5α, 6β)-17-(cyclopropylmethyl)-4,5-epoxymorphinan-3,6,14-triol (6β-naltrexol) And Its Salts From All Schedules Of Control Under The Controlled Substances Act'' and a scheduling recommendation. Following consideration of the eight factors and findings related to the substance's abuse potential, legitimate medical use, and dependence liability, the HHS recommended that 6β-naltrexol and its salts be decontrolled from all schedules of control of the CSA. The National Institute on Drug Abuse (NIDA) concurred with the recommendation.

The CSA requires the DEA to determine whether the HHS's scientific and medical evaluation, scheduling recommendation, and all other relevant data constitute substantial evidence that a substance should be scheduled. 21 U.S.C. 811(b). The DEA reviewed the scientific and medical evaluation and scheduling recommendation provided by the HHS, and all other relevant data, and completed its own eight-factor review document on 6β-naltrexol 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 6β-naltrexol 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–492.

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 6β-naltrexol. 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:

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.

According to HHS, there are no mentions of abuse of 6β-naltrexol in the National Survey on Drug Use and Health (NSDUH),[2] a survey sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA). This survey provides national and state-level data on tobacco, alcohol, and drug use, mental health and other health-related issues in the United States. The Monitoring the Future (MTF)[3] survey did not provide any data on 6β-naltrexol.

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

According to HHS, 6β-naltrexol is not currently marketed in any country. Availability is limited to research settings, and there is no evidence of diversion from legitimate drug channels. The National Forensic Laboratory Information System (NFLIS) is a DEA database that collects scientifically verified data on analyzed drug samples in State and local forensic laboratories.[4] It also includes data from the System to Retrieve Information from Drug Evidence (STRIDE), which includes data on analyzed samples from DEA laboratories.[5] There are no records of 6β-naltrexol drug cases or seized drug exhibits in NFLIS. Thus, there is no evidence of significant diversion of 6β-naltrexol.

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, 6β-naltrexol is only available in research laboratories and is not currently marketed in any country. The DEA notes that a review of scientific literature, STRIDE, STARLiMS, NFLIS, NSDUH, and MTF databases revealed no history of abuse of 6β-naltrexol. Thus, there is no evidence that individuals are taking 6β-naltrexol on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer the same.

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

[2] The National Survey on Drug Use and Health, formerly known as the National Household Survey on Drug Abuse (NHSDA), is conducted annually by the Department of Health and Human Service's 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.

[3] Monitoring the Future (MTF) is a national survey conducted by the Institute for Social Research at the University of Michigan under a grant from the National Institute on Drug Abuse (NIDA) that tracks drug use trends among American students in the 8th, 10th, and 12th grades.

[4] The National Forensic Laboratory Information System (NFLIS) represents an important resource in monitoring illicit drug abuse and trafficking, including the diversion of legally manufactured pharmaceuticals into illegal markets. NFLIS is a comprehensive information system that includes data from forensic laboratories that handle approximately 90% of an estimated 1.0 million distinct annual State and local drug analysis cases. NFLIS includes drug chemistry results from completed analyses only. While NFLIS data is not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. *See* 76 FR 77330, 77332, Dec. 12, 2011.

[5] The System to Retrieve Information from Drug Evidence database (STRIDE) reports the results of drug evidence analyzed at DEA laboratories nationwide. These drug exhibits (or items) are submitted to the laboratory as drug evidence from seizures and undercover purchases. As of October 1, 2014, STARLiMS is the new system of record for exhibits analyzed by DEA laboratories, replacing STRIDE.

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 6β-naltrexol are not related to a substance already listed as having a potential for abuse. In humans, 6β-naltrexol is the major metabolite of naltrexone, which was removed from all schedules for control under the CSA on March 6, 1975 (40 FR 10455).

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

According to HHS, 6β-naltrexol is formed when the 6-keto group of naltrexone goes through a reduction process. It is the major metabolite of naltrexone in humans, monkeys, and guinea pigs, but not in rodents. It is a considerably weaker antagonist than naltrexone and does not affect basal signaling of μ- and δ-opioid receptors in opioid-naïve and opioid-dependent states which suggests that 6β-naltrexol has neutral antagonist properties. Binding affinities (Ki) of 6β-naltrexol were 2.12 nM, 212 nM, and 7.42 nM at μ-opioid receptor, δ-opioid receptor, and κ-opioid receptor, respectively. A study found that the affinity of 6β-naltrexol for the μ-opioid receptor and κ-opioid receptor was 2- to 5-fold higher than that of naloxone and 2-fold lower than naltrexone. 6β-Naltrexol also inhibited the inverse agonist effects of naloxone in pretreated membranes. The study thus concludes that 6β-naltrexol retained neutral antagonist activity. A previous study in animal models indicates that 6β-naltrexol appears to be 1/12th to 1/185th as potent as naltrexone. Though 6β-naltrexol is lower in potency than naltrexone, it contributes to the therapeutic and adverse effects of naltrexone because it accumulates to a greater extent than naltrexone especially in chronic dosing conditions. HHS concludes that this may be attributed to 6β-naltrexol's 10-fold higher systemic exposure as compared to naltrexone. 6β-naltrexol has a longer half-life (12 to 14 hours) than that of naltrexone (4 hours).

Although 6β-naltrexol has weaker opioid receptor antagonistic properties than naltrexone, it contributes significantly to the effects of naltrexone after oral administration. 6β-Naltrexol is metabolized primarily through glucuronidation and renal secretion. 6β-Naltrexol has a lower potency than naltrexone, and its longer duration of action and higher plasma concentrations indicate that 6β-naltrexol will contribute to the therapeutic and adverse effects of naltrexone. The physiochemical properties of 6β-naltrexol suggest that it may have a preferential blockade of peripheral over central opioid receptors following a systemic administration. This selectivity for peripheral opioid receptors may allow for co-formulation with an opioid, to attenuate the peripheral side effects, such as opioid-induced changes in bowel function, and immune functions.

In the *in vitro* assay, the effect of 6β-naltrexol to inhibit morphine-induced reduction in twitch response in electrically stimulated guinea pig ileum was assessed. Results of the study showed that 6β-naltrexol was 4.5-fold more potent than naloxone and 2.8-fold more potent than naltrexone in preventing the morphine-induced reduction of twitch height of stimulated guinea pig ileum. In the *in vivo* analgesic test, naltrexone was 2 times as potent as naloxone and 185 times as potent as 6β-naltrexol in inhibiting morphine-induced antinociception in mice. Thus, 6β-naltrexol is highly potent in the guinea pig ileum *in vitro,* but much less so *in vivo* after an acute dose. The potency of 6β-naltrexol *in vivo* is also time-dependent with a longer duration of action than naloxone and naltrexone. These data are consistent with pharmacokinetic data for 6β-naltrexol with a longer terminal half-life and supports that 6β-naltrexol is likely to contribute to the efficacy of naltrexone in human subjects.

Another study that compared the activity of naltrexone and naloxone relative to 6β-naltrexol in blocking fentanyl-induced analgesia and lethality, and in precipitating withdrawal jumping in mice dependent on fentanyl reported that the potency ratio in antagonizing fentanyl-induced analgesia was 17:4:1 for naltrexone, naloxone, and 6β-naltrexol, respectively. The corresponding ratio to attenuate fentanyl-induced lethality was 13:2:1. In precipitating withdrawal, the corresponding ratio was 1107:415:1. Additionally, 6β-naltrexol pre-treatment resulted in decreased naloxone withdrawal. Thus, 6β-naltrexol produced a lower efficacy antagonist activity by blocking inverse agonist-mediated effects of naloxone. In a chronic mouse model of dependence, 6β-naltrexol was 30 and 100 times less potent than naloxone and naltrexone, respectively. 6β-Naltrexol at 1.0 mg/kg dose did not produce a withdrawal response (*e.g.,* jumping), but at 10 mg/kg dose it elicited withdrawal effect 8 hours after morphine pretreatment. 6β-Naltrexol was equipotent to naloxone in blocking morphine's anti-nociceptive effect.

In a study of developing neonatal abstinence syndrome (NAS) in pregnant mice with opioid dependence, the result found that 6β-naltrexol passed through the placenta and through the blood brain barrier (BBB) in fetal mice. A co-administration of 6β-naltrexol with morphine to postnatal mice (before day 14) inhibited withdrawal behavior at doses 20- to 500-fold lower than those used to inhibit anti-nociception in adult animals. Almost complete inhibition of withdrawal symptoms was observed at the highest dose (1 mg/kg), which correlated to 1/20th that of the morphine dose. These data support that as a neutral antagonist, 6β-naltrexol contributes through suppressing fetal withdrawal symptom.

Another study found that 6β-naltrexol was only 1/85th as potent as naltrexone in producing antagonism effects as oxymorphone-induced loss of righting reflex in rats. Another test in a spinal dog preparation showed that, 6β-naltrexol had only 1/12th to 1/15th the potency of naltrexone in producing withdrawal. 6β-Naltrexol was 1/56th as potent as naltrexone in preventing the loss of righting reflex in rats, and was 1/26th as potent as naltrexone in preventing morphine-induced Straub tail. As a weaker antagonist, 6β-naltrexol still retains moderate activity with a prolonged duration of activity in rats and mice suggesting that 6β-naltrexol may produce a longer narcotic blockade observed in humans after naltrexone administration. In another monkey study evaluating naltrexone and its metabolites of the inverse agonist activity treated with morphine (3.2 mg/day), data showed that naltrexone was 5- and 23-fold more potent than 6αnaltrexol and 6β-naltrexol without morphine pre-treatment, while in monkeys with a morphine injection, naltrexone was 8- and 71-fold more potent than 6αnaltrexol and 6β-naltrexol. The results indicate that naltrexone and 6αnaltrexol and 6β-naltrexol have qualitatively similar effects, and their potencies do not vary significantly with opioid treatment. Another study to compare the potency of naltrexone and 6β-naltrexol in monkeys revealed that naltrexone displayed 2-fold higher affinity and potency than 6β-naltrexol for the mu-opioid receptor (MOR) binding in monkey brain membranes and for MOR agonist-stimulated function, respectively. Naltrexone (0.0032–0.032 mg/kg) and 6β-naltrexol (0.32–3.2 mg/kg) retained the same potency difference in precipitating withdrawal to a similar degree. Furthermore, 6β-naltrexol failed to block naltrexone-precipitated withdrawal in morphine-dependent monkeys. These results indicate that

naltrexone and 6β-naltrexol display similar pharmacological actions with a large in vivo potency difference in monkeys such that 6β-naltrexol may play a minimal role in the therapeutic or antagonist effects of naltrexone in primates.

Clinical Studies

According to HHS, in a study involving 24 moderate-to-heavy drinkers with an oral dose of 50 mg of naltrexone, and following 3 hours of administration, the urinary levels of 6β-naltrexol were 10 times greater than those of naltrexone. A higher urine concentration of 6β-naltrexol correlated to the presence of subjective side effects, such as nausea, headache, and anxiety. The subjective side effects observed in this study are partially attributed to the effects of alcohol in combination with naltrexone. Another study found that 6β-naltrexol (ED_{50} ~3mg) significantly blocked the effect of morphine-induced gastrointestinal slowing, which is consistent with its opioid receptor antagonist pharmacology. It supports that 6β-naltrexol can block some peripheral effects of morphine while not affecting the central nervous system (CNS) analgesic effect induced by morphine. This may be because 6β-naltrexol has a difficulty in crossing the BBB and therefore has low *in vivo* CNS activity.

One clinical study of 6β-naltrexol in affecting abuse and constipation of opioids in four opioid dependent individuals on methadone maintenance therapy found that an intravenous treatment of 6β-naltrexol (0.05 mg–1.0 mg in ascending doses) through 15-minute infusions produced significantly greater Visual Analog Scale (VAS) scores of ''Any Drug Effect'' than placebo, and no significant effect was found in any other VAS measure. There was also a dose-dependent increase in gastrointestinal activity. Agonists of the μ-opioid receptor, such as methadone, are known to decrease gastrointestinal motor activity, leading to constipation. This study determined that 6β-naltrexol blocked the μ-opioid receptor agonist activity of methadone, causing an increase in locomotor activity in the gastrointestinal system. The lack of withdrawal symptoms indicated that, at these doses, 6β-naltrexol did not cross the BBB and had little effect in the CNS, thereby supporting that 6β-naltrexol is a peripherally acting μ-opioid receptor antagonist.

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

The molecular formula of 6β-naltrexol is $C_{20}H_{25}NO_4$ and the molecular weight is 343.42 g/mol. 6β-Naltrexol is formed *in vivo* when the 6-keto group of naltrexone goes through a reduction process. A structure affinity analysis indicated that 6β-naltrexol has reduced bonds in the six position of its chemical structure, which may result in its neutral antagonist activity.

According to HHS, naltrexone through the *in vivo* metabolic reduction metabolizes into two active metabolites, 6α-naltrexol and 6β-naltrexol. The metabolite, 6α-naltrexol, was found in only trace amounts in two (monkey and guinea pig) of the seven species tested. However, 6β-naltrexol was detected in the urine of all of the species tested, including humans. HHS states that 6α-naltrexol is not present as a metabolite in humans and is of little concern. Plasma concentration-time curve fit into a two compartment model with absorption showing first-order kinetics. According to another study, 6β-hydroxy epimers have little or no antinociceptive activity, while 6α-hydroxy epimers showed significant antinociceptive activity similar to the report of nalorphine and pentazocine. This study showed that 6β-naltrexol lacks analgesic activity suggesting that it does not have agonist or partial agonist properties. As stated by HHS, single and multiple administrations of 6β-naltrexol do not change its plasma kinetics. After one intramuscular injection of 6β-naltrexol (0.2 mg/kg), the time-curve of plasma concentration fits a two-compartment model with first-order absorption and it remained consistent after multiple intramuscular injections for 6β-naltrexol for 7 days.

According to HHS, naltrexone is converted to its active metabolite, 6β-naltrexol through a stereospecific reduction by dihydrodiol dehydrogenase enzymes (DD1, 2, and 4). Because of first-pass metabolism, concentrations of 6β-naltrexol are much higher than its parent molecule following oral dosing. However, when 6β-naltrexol is administered intramuscularly, hepatic biotransformation is avoided, and the arca under the curve (AUC) for 6β-naltrexol is only 2-fold higher than that of naltrexone. In contrast, following a single and multiple oral dosing of naltrexone (50 mg), 6β-naltrexol exposure was over 20-fold greater than that of the parent drug, naltrexone. In another cited study in patients with mild or moderate hepatic impairment, following a single dose of long acting naltrexone (190 mg), plasma concentrations of 6β-naltrexol were 2-fold greater than corresponding naltrexone concentrations. Thus mild or moderate hepatic impairment affect the patient's exposure to either 6β-naltrexol or naltrexone.

4. Its History and Current Pattern of Abuse

According to HHS, based on chemical and pharmacological similarities between 6β-naltrexol and naltrexone, a μ-opioid receptor antagonist that was removed from control under the CSA, it is unlikely that 6β-naltrexol would be abused. In addition, reports from Monitoring the Future, Treatment Episode Data Set, the National Survey on Drug Use and Health, poison control centers, the Drug Abuse Warning Network, NFLIS, STRIDE, and STARLiMS had no mentions of use or abuse of 6β-naltrexol.

5. The Scope, Duration, and Significance of Abuse

As mentioned in Factor 4, a comprehensive review and research on available data performed by both HHS and DEA revealed no reports of abuse of 6β-naltrexol.

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

According to both HHS and DEA's data review and as stated in Factors 4 and 5, there is no sufficient data to report any abuse of 6βnaltrexol or show the scope, duration, and significance of abuse of 6β-naltrexol. None of the available sources including Monitoring the Future, Treatment Episode Data Set, the National Survey on Drug Use and Health, poison control centers, the Drug Abuse Warning Network, NFLIS, and STRIDE capture data that examine the use or abuse of 6β-naltrexol.

7. Its Psychic or Physiological Dependence Liability

According to HHS, in a morphine dependent state, naloxone and naltrexone act as inverse agonists by suppressing basal μ-opioid receptor signaling thereby contributing to the presence of withdrawal in an opioid dependent state. 6β-Naltrexol exhibits neutral antagonist properties and results in a less severe withdrawal state. According to HHS, 6β-naltrexol and naloxone are equipotent in blocking acute morphine antinociception. In contrast, 6β-naltrexol was much less active than naloxone in eliciting withdrawal, both in acute and chronic morphine-dependence models. Yet, given at equipotent doses to naltrexone

and naloxone, 6β-naltrexol afforded a similar time course of rapid reversal of acute morphine-stimulated locomotion. Therefore, 6β-naltrexol does reach the receptor sites but fails to cause substantial withdrawal; consistent with the hypothesis that suppression of basal μ-opioid receptor signaling plays a significant role.

The HHS review stated that 6β-naltrexol has been shown to produce minimal withdrawal jumping as compared to naltrexone. A dose of 0.2 mg/kg of naltrexone and 1.0 mg/kg 6β-naltrexol are equipotent in antagonizing anti-nociceptive effects of morphine 10 to 20 minutes after administration. The 1 mg/kg dose of 6β-naltrexol did not elicit withdrawal jumping in the 72-hour time period following morphine administration, whereas the 10 mg/kg dose of naltrexone caused a withdrawal effect after 8 hours of morphine pretreatment. Another study assessing the relative potency of two opioid receptor antagonists (naltrexone and naloxone) and a neutral antagonist (6β-naltrexol) in blocking fentanylinduced analgesia and toxicity, and in precipitating withdrawal revealed that the order of potency in antagonizing analgesia and in precipitating withdrawal jumping was: Naltrexone > naloxone > 6β-naltrexol. Pretreatment with 6β-naltrexol reduced naloxone-precipitated withdrawal and supports that 6β-naltrexol acts as an antagonist.

Another HHS-cited study found that both 6β-naltrexol (10 mg/kg) and naloxone (10 mg/kg) were equipotent and 4.5- and 10-fold less potent than naltrexone (l.0 mg/kg). 6β-Naltrexol, unlike naloxone and naltrexone, at high doses produced minimal withdrawal at in an acute dependence Institute of Cancer Research (ICR) mice model. In this assay, naloxone and naltrexone produced withdrawal jumping at doses that blocked the acute effects of morphine, whereas 6β-naltrexol at 10 mg/kg (the dose that blocks the acute of effects of morphine) did not precipitate withdrawal jumping. In the chronic dependence model, 6β-naltrexol was 77-fold and 30-fold less potent than naltrexone and naloxone in producing withdrawal.

The ability of 6β-naltrexol and naltrexone to produce withdrawal in morphine-dependent and morphine-naive mice was compared. This HHS-cited study showed that naltrexone had a 10-to 100-fold greater potency than that of 6β-naltrexol. Another study compared the effects of naltrexone and 6β-naltrexol on precipitated withdrawal in morphine-dependent mice and reported that the low doses of 6β-naltrexol antagonized naltrexone precipitated withdrawal, while high doses of 6β-naltrexol were additive. This reduction in withdrawal symptoms by low doses of 6β-naltrexol is believed to be due to its neutral antagonist properties which could attenuate inverse agonist effects of naltrexone. These studies mentioned above show that 6β-naltrexol produces significantly reduced incidence of precipitated withdrawal in opioid-dependent animals compared to its parent compound, naltrexone, as well as naloxone. It may be the result of limited abilities of 6β-naltrexol in crossing the blood-brain barrier. Furthermore, there are no published reports assessing the abuse liability of 6β-naltrexol.

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

6β-Naltrexol is not considered an immediate precursor of any controlled substance.

Conclusion

Based on the consideration of the scientific and medical evaluation and accompanying recommendation of the HHS, and based on the DEA's consideration of its own eight-factor analysis, the DEA finds that these facts and all relevant data demonstrate that 6β-naltrexol does not possess abuse or dependence potential. The data from *in vitro, in vivo animal studies,* and clinical evidence indicate that 6β-naltrexol is a μ-opioid receptor antagonist and lacks abuse potential. It should be understood that the lack of currently accepted medical use in treatment in the United States is inconsequential where, as here, the substance in question is determined to have insufficient abuse potential and dependence liability to warrant control in any schedule. HHS indicated that 6β-naltrexol has no currently accepted medical use in treatment in the United States. There are no investigational new drugs and new drug applications for 6β-naltrexol. 6β-naltrexol showed no physical or psychological dependence in both non-clinical and clinical studies. Accordingly, the DEA finds that 6β-naltrexol 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 scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget (OMB) pursuant to section 3(d)(1) of Executive Order 12866 and the principles reaffirmed in Executive Order 13563.

This final rule is not an Executive Order 13771 regulatory action pursuant to Executive Order 12866 and OMB guidance.[5]

Executive Order 12988, Civil Justice Reform

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

Executive Order 13132, Federalism

This rulemaking does not have federalism implications warranting the application of Executive Order 13132. The rule does not have substantial direct effects on the States, on the relationship between the 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 Executive Order 13175. This rule does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal Government and Indian tribes, or on the distribution of power and responsibilities between the Federal Government and Indian tribes.

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

Regulatory Flexibility Act

The Acting 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 have a significant economic impact on a substantial number of small entities. The purpose of this rule is to remove 6β-naltrexol 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 6β-naltrexol. 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, 6β-naltrexol. 6β-Naltrexol is the major metabolite of naltrexone and is not currently available or marketed in any country. Due to the wide variety of unidentifiable and unquantifiable variables that potentially could influence the distribution and dispensing rates, if any, of 6β-naltrexol, the DEA is unable to determine the number of entities and small entities which might handle 6β-naltrexol. In some instances where a controlled pharmaceutical drug is removed from the schedules of the CSA, the 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, the DEA's knowledge of its registrant population forms the basis for estimating the number of affected entities and small entities. However, the DEA does not have a basis to estimate whether 6β-naltrexol is expected to be handled by persons who hold DEA registrations, by persons who are not currently registered with the DEA to handle controlled substances, or both. Therefore, the DEA is unable to estimate the number of entities and small entities who plan to handle 6β-naltrexol.

Although the 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, the DEA is specifically soliciting comments on the economic impact of this proposed rule. The DEA will revise this section if warranted after consideration of any comments received. Any person planning to handle 6β-naltrexol 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 ''Regulatory Flexibility Act'' section above, the 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. 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 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 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 and naltrexone, and their respective salts, but including the following:

* * * * *

Dated: August 6, 2019.

Uttam Dhillon,

Acting Administrator.

[FR Doc. 2019–17630 Filed 8–20–19; 8:45 am]

BILLING CODE 4410–09–P

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

24 CFR Parts 5 and 200

[Docket No. FR–6160–N–01]

Notice of Demonstration To Assess the National Standards for the Physical Inspection of Real Estate and Associated Protocols

AGENCY: Office of the Assistant Secretary for Housing; Office of the Assistant Secretary for Public and Indian Housing, U.S. Department of Housing and Urban Development.

ACTION: Notice.

SUMMARY: The shift to the National Standards for the Physical Inspection of Real Estate (NSPIRE) will further one of HUD's highest priority strategic outcomes—resident health and safety. HUD is looking at the implementation of NSPIRE as an opportunity to reduce regulatory burden through alignment and consolidation compared to either maintaining or increasing the number of standards and protocols to evaluate HUD-assisted housing across multiple programs. During this demonstration, HUD will solicit volunteers to test the NSPIRE standards and protocols as the means for assessing the physical conditions of HUD-assisted and -insured housing. The demonstration, which will include approximately 4,500 properties, will be implemented on a rolling, nationwide basis and will assess all aspects of the physical inspection line of business of the Real Estate Assessment Center—the collection, processing, and evaluation of physical inspection data and information, including a new scoring model. As the first step in the implementation of NSPIRE, HUD is soliciting comment on this proposed, voluntary demonstration. HUD will consider the comments and incorporate them into the demonstration. Subjecting the NSPIRE model to a multistage demonstration will serve as an opportunity to refine processes and ensure all mechanisms are in place to facilitate the transition to a nationwide implementation. This demonstration will also serve as the precursor to any required rulemaking.