

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Parts 1301, 1305, and 1308

[Docket No. DEA-375]

Schedules of Controlled Substances: Placement of Thiafentanil into Schedule II

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Interim final rule with request for comments.

SUMMARY: The Drug Enforcement Administration is placing the substance thiafentanil (4-(methoxycarbonyl)-4-(N-phenmethoxyacetamido)-1-[2-(thienyl)ethyl]piperidine), including its isomers, esters, ethers, salts and salts of isomers, esters and ethers as possible, into schedule II of the Controlled Substances Act. This scheduling action is pursuant to the Controlled Substances Act, as revised by the Improving Regulatory Transparency for New Medical Therapies Act which was signed into law on November 25, 2015.

DATES: The effective date of this rule is [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER]. Interested persons may file written comments on this rule in accordance with 21 U.S.C. 811(j)(3) and 21 CFR 1308.43(g). Electronic comments must be submitted, and written comments must be 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, 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 hearing pursuant to 21 CFR 1308.44 and in accordance with 21 CFR 1316.45 and/or 1316.47, as applicable. Requests for hearing and waivers of an opportunity for a hearing or to participate in a hearing must be received on or before [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: To ensure proper handling of comments, please reference “Docket No. DEA-375” on all 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 and are discouraged. 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/ODW, 8701 Morrisette Drive, Springfield, Virginia 22152.

- *Hearing requests:* All requests for hearing and waivers of participation must be sent to: Drug Enforcement Administration, Attn: Administrator, 8701 Morrisette Drive, Springfield, Virginia 22152. All requests for hearing and waivers of participation should also 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/ODW, 8701 Morrisette Drive, Springfield, Virginia 22152.

FOR FURTHER INFORMATION CONTACT: Michael J. Lewis,
Office of Diversion Control, 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 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 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, including the complete Department of Health and Human Services and Drug Enforcement Administration eight-factor analyses, to this interim final rule are available at <http://www.regulations.gov> for easy reference.

Request for Hearing, Notice of Appearance at 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 a 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. Requests for a hearing and notices of participation must conform to the requirements of 21 CFR 1308.44(a) or (b), 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 of an opportunity for a hearing must conform to the requirements of 21 CFR 1308.44(c), 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 the hearing are 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 * * *.” Requests for a hearing and waivers of participation in the hearing should be submitted to the DEA on or before the deadline specified above, using the address information provided therein.

Background, Legal Authority, and Basis for this Scheduling Action

Thiafentanil, known chemically as 4-(methoxycarbonyl)-4-(*N*-phenylmethoxyacetamido)-1-[2-(2-thienyl)ethyl]piperidine, a potent opioid, is an analogue of fentanyl. The product Thianil (thiafentanil oxalate, a salt form of thiafentanil)

was reviewed by the Food and Drug Administration (FDA) to determine whether it meets the requirements for addition to the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species (the Index) (21 U.S.C. 360ccc-1) as set forth by the Minor Use and Minor Species Animal Health Act of 2004 (MUMS Act, 2004). The MUMS Act amended the Federal Food, Drug, and Cosmetic Act (FDCA) to allow for the legal marketing of unapproved new animal drugs intended for use in minor species. In a letter from the Department of Health and Human Services (HHS) dated June 20, 2016, the DEA received notification that HHS/FDA added Thianil (thiafentanil oxalate) to the Index under section 572 of the FDCA. In this same notification, HHS/FDA stated that on June 16, 2016, HHS/FDA granted the request for the addition of Thianil to the Index under Minor Species Index File (MIF) 900000. Thianil is indicated for use in the immobilization of non-domestic, non-food-producing minor species hoofstock.

Thiafentanil will be marketed as thiafentanil oxalate, 4-(methoxycarbonyl)-4-(*N*-phenylmethoxyacetamido)-1-[2-(2-thienyl)ethyl]piperidinium oxalate. Thiafentanil should not be confused with thiofentanyl (*N*-phenyl-*N*-(1-(2-(thiophen-2-yl)ethyl)piperidin-4-yl)propionamide), which is currently listed as a controlled schedule I substance.

Under the Controlled Substances Act (CSA), as amended in 2015 by the Improving Regulatory Transparency for New Medical Therapies Act (Public Law 114-89), where the DEA receives notification from HHS that the Secretary has indexed a drug under section 572 of the FDCA, the DEA is required to issue an interim final rule controlling the drug not later than 90 days after receiving such notification from HHS. 21 U.S.C. 811(j). Accordingly, the DEA is issuing this interim final rule controlling thiafentanil.

When controlling a drug pursuant to section 811(j), the DEA must apply the scheduling criteria of subsections 811(b), (c), and (d) and section 812(b). 21 U.S.C. 811(j)(3). In accordance with these criteria, the DEA has reviewed the scientific and medical evaluation and scheduling recommendation provided by the HHS, along with all other relevant data, and completed its own eight-factor review document on thiafentanil pursuant to 21 U.S.C. 811(c). As explained below, based on these considerations, the DEA concludes that thiafentanil meets the criteria for placement in schedule II of the CSA.

On November 28, 2011, the HHS provided the DEA with its initial scientific and medical evaluation and scheduling recommendation regarding thiafentanil. Pursuant to 21 U.S.C. 811(b), this document contained an eight-factor analysis of the abuse potential of thiafentanil as a new drug, along with the HHS' recommendation to control thiafentanil and its salts under schedule II of the CSA. Subsequently, on March 23, 2016, the HHS provided the DEA with a supplement to its 2011 analysis, which indicated that the HHS/FDA planned to add Thianil (thiafentanil oxalate) to the Index for use in the immobilization of non-domestic, non-food-producing minor species hoofstock and reiterated their recommendation that thiafentanil be placed in schedule II of the CSA. By letter dated June 20, 2016, the DEA received notification from the HHS that the FDA had granted the request on June 16, 2016, for Thianil (thiafentanil oxalate) to be added to the Index.

Pursuant to 21 U.S.C. 811(j), and based on the HHS recommendation, MUMS Act indication by the HHS/FDA, and the DEA's determination, the DEA finds that thiafentanil has a high potential for abuse, a currently accepted medical use with severe

restrictions, and that abuse of thiafentanil may lead to severe psychological or physical dependence. Accordingly, the DEA is issuing this interim final rule to add thiafentanil (4-(methoxycarbonyl)-4-(*N*-phenylmethoxyacetamido)-1-[2-(2-thienyl)ethyl]piperidine) and its isomers, esters, ethers, salts and salts of isomers, esters and ethers, whenever the existence of such, to schedule II of the CSA.

Included below is a brief summary of each factor as analyzed by the HHS and the DEA, and as considered by the DEA in its scheduling action. Please note that the DEA and HHS analyses, along with the HHS supplement, are available in their entirety under “Supporting Documents” in the public docket for this interim final rule at <http://www.regulations.gov>, under Docket Number “DEA-375.” Full analysis of, and citations to, the information referenced in the summary may also be found in the supporting and related material.

1. *The Drug’s Actual or Relative Potential for Abuse:* Thiafentanil is a chemical substance that has not been marketed in the United States, however, it is approved and marketed in the Republic of South Africa as a salt form under the brand name Thianil (thiafentanil oxalate). There is no information available which details actual abuse of thiafentanil.

According to the HHS, thiafentanil is a synthetic analogue of fentanyl and is structurally related to other fentanyl-like opioids such as sufentanil (schedule II) and carfentanil (schedule II). It acts as a potent μ -opioid receptor agonist and produces strong morphine-like effects in animals. It is only intended for the immobilization of non-domestic, non-food-producing minor species hoofstock. Thiafentanil has been used in a manner similar to other opioid immobilizing agents such as etorphine hydrochloride

(schedule II) and carfentanil (schedule II), which are approved only for veterinary use as animal immobilization agents. The abuse potential of thiafentanil has not been evaluated in humans or in animal behavioral models that are predictors of abuse by humans.

Because thiafentanil shares chemical and pharmacological similarities with schedule II fentanyl and its analogues, the abuse potential of thiafentanil is considered similar to that of schedule II opioid substances such as sufentanil and carfentanil.

Pharmacologically, as a potent μ opioid receptor agonist, thiafentanil is slightly less potent than carfentanil, which is 100 times more potent than fentanyl and 10,000 times more potent than morphine. Thiafentanil is a potent fentanyl analogue. Thus, it is reasonable to assume that there will be potentially significant diversion of thiafentanil from legitimate channels by people who have access to it, and that thiafentanil would be used without medical advice, therefore causing substantial hazards to the users or to the safety of the community if not controlled. The chemical and potent opioid-like pharmacological properties of thiafentanil predict that its risk to the public health is likely to be similar to fentanyl (schedule II) and its analogues such as carfentanil (schedule II), sufentanil (schedule II) and alpha-methylfentanyl (schedule I).

2. *Scientific Evidence of the Drug's Pharmacological Effects, if Known:* According to HHS' scientific and medical review, there are no data on the effects of thiafentanil in humans. Thiafentanil's effects in humans are predicted from its effects in animals and its chemical and pharmacological similarity to other schedule II potent opioids such as fentanyl and carfentanil.

The HHS eight-factor review document described a study directly comparing the immobilizing effects of thiafentanil (15 mg) and carfentanil (2 or 4 mg) in elk in which

thiafentanil produced a faster immobilization effect (0.7 to 2.2 minutes) than carfentanil. In addition, the elk returned to standing 0.9 to 1.4 minutes faster under the thiafentanil condition. This study appears to support a faster immobilization and recovery time with thiafentanil relative to carfentanil. However, the authors stated that the role of the increased dose of thiafentanil is unknown.

Animal studies described by the HHS demonstrated that the effects of thiafentanil and carfentanil are completely reversed by naltrexone. As a μ -opioid receptor antagonist, naltrexone can reverse the effects of a variety of opioid drugs including thiafentanil and carfentanil. Those studies suggest that thiafentanil possesses a neuro-pharmacological mechanism of action similar to other schedule II opioid drugs with a high abuse potential.

According to HHS' review, Thianil (thiafentanil) is currently approved and registered for use in the Republic of South Africa. Thiafentanil oxalate is suggested as a drug of choice in the capture of exotic and ungulate wildlife species.

3. *The State of Current Scientific Knowledge Regarding Thiafentanil:* The chemical name of free base thiafentanil is 4-(methoxycarbonyl)-4-(*N*-phenylmethoxyacetamido)-1-[2-(2-thienyl)ethyl]piperidine. It has a molecular formula of $C_{22}H_{28}N_2O_4S$ and a molecular weight of 416.52 g/mol with a Chemical Abstract Registry Number (CAS) of 101345-60-2. Thiafentanil oxalate is also known as A3080 with a CAS number of 101365-73-5 and has a molecular formula of $C_{24}H_{30}N_2O_8S$ with a molecular weight of 506.57 g/mol. Thiafentanil oxalate is a white crystalline powder with a melting point of 190–192°C and its salt crystalizes from absolute alcohol. Thiafentanil should not be confused with thiofentanyl (*N*-phenyl-*N*-(1-(2-(thiophen-2-yl)ethyl)piperidin-4-yl)propionamide), which is currently listed as a schedule I substance.

4. *Its History and Current Pattern of Abuse:* According to the HHS' review, there are no reports of actual abuse and misuse of thiafentanil. This may be due to the limited use of thiafentanil as an immobilizing agent by trained veterinarians.

Current data from the National Forensic Laboratory System (NFLIS),¹ the System to Retrieve Information from Drug Evidence (STRIDE)², and the STARLiMS databases show that there is no evidence of law enforcement encounters of thiafentanil in the United States. However, thiafentanil's pharmacological and structural properties suggest that its pattern of abuse would be similar to other potent schedule II μ -opioid receptor agonists such as fentanyl and carfentanil.

5. *The Scope, Duration, and Significance of Abuse:* An assessment of the scope, duration, and significance of thiafentanil abuse is not available since it has only been used in a limited market. However, as stated in the HHS review, the structural and pharmacological properties of thiafentanil suggest that it could lead to an abuse pattern with a scope, duration, and significance of abuse similar to that observed with other opioid drugs and opioid analogues if it were marketed in a non-controlled status or were the subject of clandestine synthesis. The HHS and DEA note that thiafentanil is not known to be or to have been the subject of abuse in the United States.

¹ The National Forensic Laboratory System (NFLIS) is a program of the DEA, Office of Diversion Control. NFLIS systematically collects drug identification results and associated information from drug cases submitted to and analyzed by State and local forensic laboratories. 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.

² The System to Retrieve Information from Drug Evidence (STRIDE) is a database of drug exhibits sent to DEA laboratories for analysis. Exhibits from the database are from the DEA, other federal agencies, and local law enforcement agencies. Reporting via STRIDE ceased on September 30, 2014. STRIDE was succeeded by STARLiMS.

6. *What, if any, Risk There is to the Public Health:* The HHS review indicates that thiafentanil presents a significant risk to the public health and, in this vein, that thiafentanil should only be used in certain animals for very limited purposes and with extreme caution. Based on the review of the structural and pharmacological properties of thiafentanil, the HHS concluded that the abuse of thiafentanil is likely to pose a similar risk to public health as that of other potent opioid drugs such as sufentanil (schedule II), fentanyl (schedule II), carfentanil (schedule II) and clandestinely synthesized alpha-methylfentanyl (schedule I). Thus, inappropriate use of thiafentanil poses a high risk to the public health. Among other things, HHS noted that as a fentanyl derivative, and assuming that thiafentanil can be aerosolized, the use of thiafentanil presents a significant risk to the public health.

HHS described that thiafentanil's labeling indicates that it is solely intended for use by zoologic, wildlife, or exotic animal veterinarians or field biologists who have received training and are supervised by veterinarians. The sponsor recommends the use of handling protocols similar to those in place for other scheduled potent opioids such as carfentanil. HHS further indicated that thiafentanil should be handled in teams consisting of at least two individuals knowledgeable about the hazards of working with potent μ -opioid agonist substances. Personal protective equipment such as latex gloves and protective eyewear should be used and syringes must be disposed of properly. If exposure to thiafentanil occurs in a remote or distant environment, veterinary naltrexone is recommended for use as a reversal agent. The label information will further state that thiafentanil must never be used unless an adequate amount of reversal agent (naltrexone hydrochloride) is immediately available.

HHS also describes the risk of thiafentanil intoxication upon ingestion of animals immobilized with thiafentanil. The label information states that thiafentanil is not intended for human or animal consumption or in non-food producing minor species that become eligible for consumption by humans or food-producing animals. Because thiafentanil, similar to carfentanil, etorphine hydrochloride and diprenorphine, is a potent μ -opioid receptor agonist, it will be subject to specialized handling, distribution and storage procedures similar to those applicable for carfentanil, etorphine hydrochloride and diprenorphine as set forth in 21 CFR parts 1301 and 1305. As a result, this interim final rule revises 21 CFR 1301.74(g), 1301.75(e), 1305.07 introductory text and paragraph (a), and 1305.17(d) to include “thiafentanil.”

7. Its Psychic or Physiological Dependence Liability: HHS’ review states that the structural and pharmacological properties of thiafentanil suggest that it possesses a psychic and physiological dependence liability that is similar to other schedule II related μ -opioid receptor agonist drugs such as sufentanil, fentanyl and carfentanil.

As cited by the HHS review, a double-blind abuse liability study examining intravenous fentanyl, buprenorphine, heroin, morphine, and oxycodone in methadone-maintained patients reported that fentanyl produced subjective effects similar to heroin (schedule I) on several outcome measures indicating that the two drugs produce similar subjective effects. It also demonstrates the psychic dependence liability of fentanyl, and thiafentanil is expected to produce effects similar to fentanyl and to present a similar risk of psychic and physiological dependence. There has been a major increase in abuse of opioids analgesics in the United States (HHS review document, 2011; Compton and

Volkow, 2006). Thiafentanil, similar to these opioid analgesics, presents a risk of severe psychic and physiological dependence.

8. *Whether the Substance is an Immediate Precursor of a Substance Already Controlled under the CSA:* Thiafentanil is not considered an immediate precursor of any controlled substance.

Determination of Appropriate Schedule

The CSA lists the findings required to place a drug or other substance in any particular schedule (I, II, III, IV, or V). 21 U.S.C. 812(b). After consideration of the analysis and recommendation of the Assistant Secretary for Health of the HHS and review of all available data, the Acting Administrator of the DEA, pursuant to 21 U.S.C. 812(b)(2), finds that:

1. Thiafentanil has a high potential for abuse. Based on its structural and pharmacological properties, thiafentanil has an abuse potential that is comparable to other schedule II opioid drugs such as fentanyl, carfentanil, and sufentanil;
2. FDA determined that Thianil (thiafentanil oxalate) meets the requirements for addition to the Index as set forth by the MUMS Act, 2004 and accordingly added Thianil (thiafentanil oxalate) to the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species (the Index) under section 572 of the Federal Food, Drug, and Cosmetic Act. Thianil (thiafentanil oxalate) will be legally marketed in the United States and will have an accepted medical use with severe restrictions;³ and

³ According to the HHS analysis, “[u]se of a new animal indexed drug is subject to significant restrictions. For example, use of an indexed new animal drug for minor species is limited to a minor species for which there is a reasonable certainty that the animal or edible products from the animal will not be consumed by humans or food producing animals. 21 U.S.C. § 360ccc-1 (a)(1). The requester must label, distribute, and promote the new animal drug in accordance with the Index entry, and the FDA may remove a new animal

3. Due to the chemical and pharmacological similarities of thiafentanil to other schedule II fentanyl derivatives, abuse of thiafentanil may lead to severe psychological or physical dependence.

Based on these findings, the Acting Administrator of the DEA concludes that thiafentanil, including its isomers, esters, ethers, salts and salts of isomers, esters and ethers whenever the existences of such isomers, esters, ethers, and salts is possible warrants control in schedule II of the CSA. 21 U.S.C. 812(b)(2).

Requirements for Handling Thiafentanil

Thiafentanil is subject to the CSA's schedule II regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, reverse distribution, dispensing, importing, exporting, research, and conduct of instructional activities and chemical analysis with, and possession involving schedule II substances, including the following:

1. *Registration.* Any person who desires to handle thiafentanil (manufacture, distribute, reverse distribute, dispense, import, export, engage in research, or conduct instructional activities or chemical analysis with, or possess), must be registered with the DEA to conduct such activities pursuant to 21 U.S.C. 822, 823, 957, and 958 and in accordance with 21 CFR parts 1301 and 1312.

drug from the Index if the conditions and limitations of use have not been followed. 21 U.S.C. 360ccc-1 (d)(1)(G); (f)(1)(F). The labeling of an indexed new animal drug must prominently state that the extra-label use of the product is prohibited. 21 U.S.C. 360ccc-1(h). Such restrictions are not imposed upon approved human or animal drugs.”

2. *Quota.* Only registered manufacturers are permitted to manufacture thiafentanil in accordance with a quota assigned pursuant to 21 U.S.C. 826 and in accordance with 21 CFR part 1303.

3. *Disposal of stocks.* Upon obtaining a schedule II registration to handle thiafentanil, and if subsequently, any person who does not desire or is not able to maintain a schedule II registration must surrender all quantities of currently held thiafentanil, or may transfer all quantities of currently held thiafentanil to a person registered with the DEA in accordance with 21 CFR part 1317, in addition to all other applicable federal, state, local, and tribal laws.

4. *Security.* Thiafentanil is subject to schedule II security requirements and must be handled and stored pursuant to 21 U.S.C. 821 and 823, and in accordance with 21 CFR 1301.71–1301.93.

5. *Labeling and Packaging.* All labels, labeling, and packaging for commercial containers of thiafentanil must comply with 21 U.S.C. 825 and 958(e), and be in accordance with 21 CFR part 1302. In addition, thiafentanil is subject to additional labeling requirements provided by FDA. Thiafentanil must be labeled, distributed, and promoted in accordance with the Index entry of the new animal drug and the FDA may remove a new animal drug from the Index if the conditions and limitations of use have not been followed. 21 U.S.C. 360ccc-1(d)(1)(G); (f)(1)(F). The labeling of an indexed new animal drug must prominently state that the extra-label use of the product is prohibited. 21 U.S.C. 360ccc-1(h).

6. *Inventory.* Every DEA registrant who desires to possess any quantity of thiafentanil must take an inventory of thiafentanil on hand, pursuant to 21 U.S.C. 827 and 958, and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11.

Any person who becomes registered with the DEA to handle thiafentanil must take an initial inventory of all stocks of controlled substances (including thiafentanil) on hand on the date the registrant first engages in the handling of controlled substances, pursuant to 21 U.S.C. 827 and 958, and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11.

After the initial inventory, every DEA registrant must take a new inventory of all stocks of controlled substances (including thiafentanil) on hand every two years, pursuant to 21 U.S.C. 827 and 958, and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11.

7. *Records and Reports.* Every DEA registrant must maintain records and submit reports for thiafentanil, or products containing thiafentanil, pursuant to 21 U.S.C. 827 and 958(e), and in accordance with 21 CFR parts 1304, 1312, and 1317.

8. *Orders for thiafentanil.* Every DEA registrant who distributes thiafentanil is required to comply with order form requirements, pursuant to 21 U.S.C. 828, and in accordance with 21 CFR part 1305.

9. *Prescriptions and other dispensing.* All prescriptions for thiafentanil or products containing thiafentanil must comply with 21 U.S.C. 829, and be issued in accordance with 21 CFR parts 1306 and 1311, subpart C. Moreover, given that thiafentanil is not the subject of an approved new drug application under the FDCA, and that it is only allowed under the MUMS Act amendments to the FDCA to be marketed for extremely limited use in minor species, DEA would not consider any dispensing of thiafentanil for human use

to be for a legitimate medical purpose within the meaning of the CSA. Likewise, DEA would not consider any dispensing of thiafentanil for animal use beyond the scope of the drug's labeling authorized under the MUMS Act amendments to the FDCA to be for a legitimate medical purpose within the meaning of the CSA.

10. *Manufacturing and Distributing.* In addition to the general requirements of the CSA and DEA regulations that are applicable to manufacturers and distributors of schedule II controlled substances, such registrants should be advised that (consistent with the foregoing considerations) any manufacturing or distribution of thiafentanil may only be for the legitimate purposes consistent with the drug's labeling authorized under the MUMS Act, or for research activities authorized by the FDCA and CSA.

11. *Importation and Exportation.* All importation and exportation of thiafentanil must be in compliance with 21 U.S.C. 952, 953, 957, and 958, and in accordance with 21 CFR part 1312.

12. *Liability.* Any activity involving thiafentanil not authorized by, or in violation of, the CSA or its implementing regulations, is unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

Regulatory Analyses

Administrative Procedure Act

Public Law 114-89 was signed into law, amending 21 U.S.C. 811. This amendment provides that in cases where a new drug is (1) approved or indexed by the Department of Health and Human Services (HHS) and (2) HHS recommends control in CSA schedule II-V, the DEA shall issue an interim final rule scheduling the drug within 90 days. Additionally, the law specifies that the rulemaking shall become immediately effective as

an interim final rule without requiring the DEA to demonstrate good cause. Therefore, the DEA has determined that the notice and comment requirements of section 553 of the APA, 5 U.S.C. 553, do not apply to this scheduling action.

Executive Orders 12866, Regulatory Planning and Review, and 13563, Improving Regulation and Regulatory Review

In accordance with Public Law 114-89, this scheduling action is subject to formal rulemaking procedures performed “on the record after opportunity for a hearing,” which are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth the procedures and criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget (OMB) pursuant to section 3(d)(1) of Executive Order 12866 and the principles reaffirmed in Executive Order 13563.

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 to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132, Federalism

This rulemaking does not have federalism implications warranting the application of Executive Order 13132. The rule does not have substantial direct effects on the States, on the relationship between the national government and the States, or on 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. 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

In accordance with 5 U.S.C. 603(a), “[w]henver an agency is required by [5 U.S.C. 553], or any other law, to publish general notice of proposed rulemaking for any proposed rule, or publishes a notice of proposed rulemaking for an interpretive rule involving the internal revenue laws of the United States, the agency shall prepare and make available for public comment an initial regulatory flexibility analysis.” As noted in the above discussion regarding applicability of the Administrative Procedure Act, the DEA has determined that the notice and comment requirements of section 553 of the APA, 5 U.S.C. 553, do not apply to this scheduling action. Consequently, the RFA does not apply to this interim final rule.

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 of 1995

This action does not impose a new collection of information requirement under the Paperwork Reduction Act of 1995. 44 U.S.C. 3501–3521. This action would not impose recordkeeping or reporting requirements on State or local governments, individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Congressional Review Act

This rule is not a major rule as defined by section 804 of the Small Business Regulatory Enforcement Fairness Act of 1996 (Congressional Review Act (CRA)). This rule will not result in: an annual effect on the economy of \$100,000,000 or more; a major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; or significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of U.S.-based companies to compete with foreign based companies in domestic and export markets. However, pursuant to the CRA, the DEA has submitted a copy of this interim final rule to both Houses of Congress and to the Comptroller General.

List of Subjects

21 CFR Part 1301

Administrative practice and procedure, Drug traffic control, Security measures.

21 CFR Part 1305

Drug traffic control, Reporting and recordkeeping requirements.

21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, the DEA amends 21 CFR parts 1301, 1305 and 1308 as follows:

PART 1301—REGISTRATION OF MANUFACTURERS, DISTRIBUTORS, AND DISPENSERS OF CONTROLLED SUBSTANCES

1. The authority citation for 21 CFR part 1301 continues to read as follows:

Authority: 21 U.S.C. 821, 822, 823, 824, 831, 871(b), 875, 877, 886a, 951, 952, 953, 956, 957, 958, 965.

2. In § 1301.74, revise paragraph (g) to read as follows:

§ 1301.74 Other security controls for non-practitioners; narcotic treatment programs and compounders for narcotic treatment programs.

* * * * *

(g) Before the initial distribution of thiafentanil, carfentanil, etorphine hydrochloride and/or diprenorphine to any person, the registrant must verify that the person is authorized to handle the substance(s) by contacting the Drug Enforcement Administration.

* * * * *

3. In § 1301.75, revise paragraph (e) to read as follows:

§ 1301.75 Physical security controls for practitioners.

* * * * *

(e) Thiafentanil, carfentanil, etorphine hydrochloride and diprenorphine shall be stored in a safe or steel cabinet equivalent to a U.S. Government Class V security container.

**PART 1305—ORDERS FOR SCHEDULE I AND II CONTROLLED
SUBSTANCES**

4. The authority citation for 21 CFR part 1305 continues to read as follows:

Authority: 21 U.S.C. 821, 828, 871(b), unless otherwise noted.

5. In § 1305.07, revise the introductory text and paragraph (a) to read as follows:

§ 1305.07 Special procedure for filling certain orders.

A supplier of thiafentanil, carfentanil, etorphine hydrochloride, or diprenorphine, if he or she determines that the purchaser is a veterinarian engaged in zoo and exotic animal practice, wildlife management programs, or research, and is authorized by the Administrator to handle these substances, may fill the order in accordance with the procedures set forth in § 1305.17 except that:

(a) A DEA Form 222 or an electronic order for thiafentanil, carfentanil, etorphine hydrochloride, and diprenorphine must contain only these substances in reasonable quantities.

* * * * *

6. In § 1305.17, revise paragraph (d) to read as follows:

§ 1305.17 Preservation of DEA Forms 222.

* * * * *

(d) The supplier of thiafentanil, carfentanil, etorphine hydrochloride, and diprenorphine must maintain DEA Forms 222 for these substances separately from all other DEA Forms 222 and records required to be maintained by the registrant.

PART 1308—SCHEDULES OF CONTROLLED SUBSTANCES

7. 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.

8. In § 1308.12, add paragraph (c)(29) to read as follows:

§ 1308.12 Schedule II.

* * * * *

(c) * * *

(29) Thiafentanil..... **9729**

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Dated: August 18, 2016.

Chuck Rosenberg,

Acting Administrator.

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