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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-565]

Schedules of Controlled Substances: Placement of cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl into Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Drug Enforcement Administration proposes placing cyclopentyl fentanyl (*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylcyclopentanecarboxamide), isobutyryl fentanyl (*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylisobutyramide), *para*-chloroisobutyryl fentanyl (*N*-(4-chlorophenyl)-*N*-(1-phenethylpiperidin-4-yl)isobutyramide), *para*-methoxybutyryl fentanyl (*N*-(4-methoxyphenyl)-*N*-(1-phenethylpiperidin-4-yl)butyramide), and valeryl fentanyl (*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylpentanamide), including their isomers, esters, ethers, salts, and salts of isomers, esters and ethers whenever the existence of such isomers, esters, ethers and salts is possible, in schedule I of the Controlled Substances Act. If finalized, this action would make permanent the existing regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances on persons who handle (manufacture, distribute, import, export, engage in research, conduct instructional activities or chemical analysis, or possess), or propose to handle cyclopentyl fentanyl,

isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl.

DATES: Comments must be submitted electronically or postmarked on or before [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER].

Interested persons may file a request for hearing or waiver of hearing pursuant to 21 CFR 1308.44 and in accordance with 21 CFR 1316.45 and/or 1316.47, as applicable. Requests for hearing and waivers of an opportunity for a hearing or to participate in a hearing must be received on or before [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: Interested persons may file written comments on this proposal in accordance with 21 CFR 1308.43(g). Commenters should be aware that the electronic Federal Docket Management System will not accept comments after 11:59 p.m. Eastern Time on the last day of the comment period. To ensure proper handling of comments, please reference “Docket No. DEA-565” on all electronic and written correspondence, including any attachments.

- *Electronic comments:* 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 to attach a file for lengthier comments. Please go to <http://www.regulations.gov> and follow the online instructions at that site for submitting comments. Upon completion of your submission you will receive a Comment Tracking Number for your comment. Please be aware that submitted comments are not instantaneously available for public view on Regulations.gov. If you have received a Comment Tracking Number, your

comment has been successfully submitted and there is no need to resubmit the same comment.

- *Paper comments:* Paper comments that duplicate the electronic submission are not necessary. Should you wish to mail a paper comment *in lieu of* an electronic comment, it should be sent via regular or express mail to: Drug Enforcement Administration, Attn: DEA Federal Register Representative/DRW, 8701 Morrisette Drive, Springfield, Virginia 22152.

- *Hearing requests:* All requests for hearing and waivers of participation must be sent to: Drug Enforcement Administration, Attn: Administrator, 8701 Morrisette Drive, Springfield, Virginia 22152. All requests for hearing and waivers of participation should be sent to: Drug Enforcement Administration, Attn: Hearing Clerk/LJ, 8701 Morrisette Drive, Springfield, Virginia 22152; and (2) Drug Enforcement Administration, Attn: DEA Federal Register Representative/DRW, 8701 Morrisette Drive, Springfield, Virginia 22152.

FOR FURTHER INFORMATION CONTACT: Scott A. Brinks, 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 confidential business information to be redacted within the comment.

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

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

Request for Hearing or Waiver of Participation in a Hearing

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). 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 person's interests in the proposed scheduling action, whether the person is adversely affected or aggrieved, and the objections or issues, if any, concerning which the person desires to be heard at a hearing. 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.

Legal Authority

The Controlled Substances Act (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 proposed action is supported by a recommendation from the Assistant Secretary for Health of the HHS (Assistant Secretary) and an evaluation of all other relevant data by the DEA. If finalized, this action would make permanent the existing temporary regulatory controls and

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, 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.

administrative, civil, and criminal sanctions of schedule I controlled substances on any person who handles or proposes to handle cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl.

Background

On February 1, 2018, DEA published an order in the *Federal Register* amending 21 CFR 1308.11(h) to temporarily place cyclopentyl fentanyl (*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylcyclopentanecarboxamide), isobutyryl fentanyl (*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylisobutyramide), *para*-chloroisobutyryl fentanyl (*N*-(4-chlorophenyl)-*N*-(1-phenethylpiperidin-4-yl)isobutyramide), *para*-methoxybutyryl fentanyl (*N*-(4-methoxyphenyl)-*N*-(1-phenethylpiperidin-4-yl)butyramide), and valeryl fentanyl (*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylpentanamide), along with two other substances², in schedule I of the CSA pursuant to the temporary scheduling provisions of 21 U.S.C. 811(h). 83 FR 4580. That temporary scheduling order was effective on the date of publication, and was based on findings by the former Acting Administrator of DEA (Acting Administrator) that the temporary scheduling of these seven substances was necessary to avoid an imminent hazard to public safety pursuant to 21 U.S.C. 811(h)(1). Section 201(h)(2) of the CSA, 21 U.S.C. 811(h)(2), requires that the temporary control of these substances expire two years from the effective date of the scheduling order, which was February 1, 2018. However, the CSA also provides that during the pendency of proceedings under 21 U.S.C. 811(a)(1) with respect to the substance, the temporary scheduling of that substance could be extended for up to one year. Proceedings for the

² Those two other substances, ocfentanil (*N*-(2-fluorophenyl)-2-methoxy-*N*-(phenethylpiperidin-4-yl)acetamide) and *para*-fluorobutyryl fentanyl (*N*-(4-fluorophenyl)-*N*-(1-phenethylpiperidin-4-yl)butyramide), were subsequently permanently placed in schedule I on November 29, 2018 (83 FR 61320) and October 25, 2019 (84 FR 57327), respectively, pursuant to 21 USC 811(d)(1).

scheduling of a substance under 21 U.S.C. 811(a) may be initiated by the Attorney General (delegated to the Administrator of the DEA pursuant to 28 CFR 0.100) on his own motion, at the request of the Secretary of HHS³, or on the petition of any interested party. An extension of the existing temporary order is being ordered by the Acting Administrator in a separate action, and is published elsewhere in this issue of the *Federal Register*.

The Acting Administrator, on his own motion pursuant to 21 U.S.C. 811(a), is initiating proceedings under 21 U.S.C. 811(a)(1) to permanently schedule cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl. DEA has gathered and reviewed the available information regarding the pharmacology, chemistry, trafficking, actual abuse, pattern of abuse, and the relative potential for abuse for these substances. On November 5, 2018, the Acting Administrator submitted a request to the Assistant Secretary to provide DEA with a scientific and medical evaluation of available information and a scheduling recommendation for cyclopropyl fentanyl, *para*-fluorobutyryl fentanyl, cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl, in accordance with 21 U.S.C. 811(b) and (c).

In a letter dated September 6, 2019, DEA notified HHS that it no longer needed scientific and medical evaluations for cyclopropyl fentanyl and *para*-fluorobutyryl fentanyl. Subsequently, DEA permanently placed these two substances in schedule I of the CSA on October 25, 2019, pursuant to 21 U.S.C. 811(d)(1). (84 FR 57323).

³ Because the Secretary of HHS has delegated to the Assistant Secretary the authority to make domestic drug scheduling recommendations, for purposes of this proposed rulemaking, all subsequent references to “Secretary” have been replaced with “Assistant Secretary.”

On November 12, 2019, the Assistant Secretary submitted HHS's scientific and medical evaluation and scheduling recommendation⁴ for cyclopropyl fentanyl and *para*-fluorobutyryl fentanyl, cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl to the Acting Administrator. Upon receipt of the scientific and medical evaluation and scheduling recommendation from the HHS, in accordance with 21 U.S.C. 811(c), the DEA reviewed the documents and all other relevant data, and conducted its own eight-factor analysis of the abuse potential of cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl.

Proposed Determination to Permanently Schedule Cyclopentyl fentanyl, Isobutyryl fentanyl, *para*-Chloroisobutyryl fentanyl, *para*-Methoxybutyryl fentanyl, and Valeryl fentanyl

As discussed in the background section, the Acting Administrator is initiating proceedings, pursuant to 21 U.S.C. 811(a)(1), to add cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl permanently to schedule I. DEA has reviewed the scientific and medical evaluation and scheduling recommendation received from HHS, and all other relevant data and conducted its own eight-factor analysis of the abuse potential of these five substances pursuant to 21 U.S.C. 811(c). 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 proposed scheduling action. Please note that both DEA 8-Factor and HHS 8-Factor

⁴ Although HHS provided information on cyclopropyl fentanyl and *para*-fluorobutyryl fentanyl, these two substances will not be discussed in this notice of proposed rulemaking because they are already permanently controlled.

analysis and the Assistant Secretary's November 12, 2019, letter are available in their entirety under the tab "Supporting Documents" of the public docket for this action at <http://www.regulations.gov> under Docket Number "DEA-565."

1. *The Drug's Actual or Relative Potential for Abuse*: The term "abuse" is not defined in the CSA. However, the legislative history of the CSA suggests DEA consider the following criteria when determining whether a particular drug or substance has a potential for abuse⁵:

- a) *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; or*
- b) *There is significant diversion of the drug or drugs containing such a substance from legitimate drug channels; or*
- c) *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; or*
- d) *The drug or drugs containing such a substance are new drugs so related in their action to a drug or drugs already listed as having a potential for abuse to make it likely that the drug will have the same potentiality for abuse as such drugs, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.*

The abuse potential of cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl is associated with its pharmacological similarity to other schedule I and II mu-opioid

⁵ Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. REP. NO. 91-1444, 91st Cong., Sess. 1 (1970); *reprinted in* 1970 U.S.C.C.A.N. 4566, 4603.

receptor agonist substances which have a high potential for abuse. Similar to morphine, fentanyl and several schedule I opioid substances that are structurally related to fentanyl, cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl have been shown to bind and act as mu-opioid receptor agonists.

Cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl have no approved medical use in the United States and have been encountered on the illicit drug market. The use of cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl has been associated with adverse outcomes to include intoxications for *para*-chloroisobutyryl fentanyl and *para*-methoxybutyryl fentanyl. Because these five substances are not Food and Drug Administration (FDA) approved drug products, a practitioner may not legally prescribe them, and these substances cannot be dispensed to an individual. Therefore, the use of cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl is without medical advice, and accordingly, leads to the conclusion that these five substances are abused for their opioid-like properties. There are no legitimate channels for these five substances to be marketed as FDA-approved drug products but they are available for purchase from legitimate chemical companies to be used in scientific research. However, despite the limited legitimate use of these substances, reports from public health and law enforcement indicate that cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl are being abused and taken in amounts sufficient to create a

hazard to an individual's health. Data from forensic databases can be used as an indicator of illicit activity with drugs and abuse⁶ within the United States. According to drug seizure data from STRIDE and STARLiMS⁷ and the National Forensic Laboratory Information System (NFLIS)⁸, cyclopentyl fentanyl, isobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl are being encountered in the United States. Although there have been no law enforcement encounters for *para*-chloroisobutyryl fentanyl thus far, this substance poses the same qualitative public health risks as heroin, fentanyl, and other opioid analgesic substances.

2. *Scientific Evidence of the Drug's Pharmacological Effects, if Known:* Cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl are pharmacologically similar to other schedule I and schedule II mu-opioid receptor agonist substances. Non-clinical and clinical studies conducted on abuse potential of mu-opioid receptor agonists such as morphine and fentanyl indicate that these substances share discriminative stimulus effects and have reinforcing properties. Similar to schedule I and II opioid analgesics, cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl bind to and activate the mu-opioid receptor. Additionally,

⁶ While law enforcement 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.

⁷ October 1, 2014, the DEA implemented STARLiMS (a web-based, commercial laboratory information management system) to replace the System to Retrieve Information from Drug Evidence (STRIDE) as its laboratory drug evidence data system of record. DEA laboratory data submitted after September 30, 2014, are repositied in STARLiMS. STRIDE/STARLiMS data were queried on 11/20/2019.

⁸ NFLIS is a DEA program and a national forensic laboratory reporting system that systematically collects results from drug chemistry analyses conducted by state and local forensic laboratories in the United States. The NFLIS database also contains Federal data from U.S. Customs and Border Protection (CBP). NFLIS only includes drug chemistry results from completed analyses. NFLIS data were queried 11/20/2019. NFLIS is still reporting data from 2018-2019 due to normal lag time in reporting.

behavioral studies in animals demonstrate that similar to fentanyl and morphine, cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl produce analgesic effects. Pre-treatment with naltrexone, an opioid antagonist, attenuated analgesic effects of cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, valeryl fentanyl, fentanyl, and morphine. Thus, it is concluded from *in vitro* and *in vivo* pharmacological studies that effects of cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl are similar to that of fentanyl and morphine and mediated by mu-opioid receptor agonism.

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

Substance: Cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl are synthetic opioids in the 4-anilidopiperidine structural class which includes fentanyl. These five substances differ in chemical structure from fentanyl by modification at the acyl group. Fentanyl is substituted with an ethyl group at this position. Modifications of this group include cycloalkyl groups (cyclopentyl fentanyl), branched alkyl groups (isobutyryl fentanyl and *para*-chloroisobutyryl fentanyl), or other linear alkyl groups by adding one methylene group to give a propyl group (*para*-methoxybutyryl fentanyl) or two methylene groups to give a butyl group (valeryl fentanyl). In addition to modification of the acyl group, *para*-methoxybutyryl fentanyl and *para*-chloroisobutyryl fentanyl are substituted at the *para*-position of the *N*-phenyl ring with a methoxy group or a chlorine atom, respectively.

No study has been undertaken to evaluate the efficacy, toxicology, and safety of cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, or valeryl fentanyl in humans. It can be inferred from medical examiner reports and data obtained from animal studies that these five substances have sufficient distribution to the brain to produce depressant effects similar to that of mu-opioid receptor agonists.

There are no FDA-approved marketing applications for drug products containing cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *Para*-methoxybutyryl fentanyl, or valeryl fentanyl for any therapeutic indication in the United States. Moreover, there are no clinical studies or petitioners which have claimed an accepted medical use in the United States for these substances.

4. *Its History and Current Pattern of Abuse:* Cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl have recently been encountered by law enforcement and/or public health officials in the United States or elsewhere. Evidence suggests that the pattern of abuse of these five substances parallels that of prescription opioid analgesics. The first reports of cyclopentyl fentanyl and valeryl fentanyl in the United States were in 2015. *para*-Methoxybutyryl fentanyl followed in 2016 and isobutyryl fentanyl was first reported in 2017. While there are no drug seizure reports for *para*-chloroisobutyryl fentanyl, one intoxication was associated with this substance in Sweden.

5. *The Scope, Duration, and Significance of Abuse:* Cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl, similar to other substances structurally related to fentanyl, are often used as

recreational drugs. The recreational use of these substances continues to be of significant concern in the United States. These substances are distributed to users often with unpredictable outcomes. Currently, the United States is in the midst of an illicit opioid abuse epidemic.

NFLIS and STARLiMS data indicate that law enforcement encounters for isobutyryl fentanyl and valeryl fentanyl have increased over the years, with valeryl fentanyl nearly doubling from 2018 to 2019. Cyclopentyl fentanyl was found in three exhibits in 2017 and *para*-methoxybutyryl fentanyl was found in one exhibit in 2016; these two substances haven't been reported since. *para*-Chloroisobutyryl fentanyl has not been found in any drug seizure reports. DEA notes that the data from pharmacological testing of cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl are consistent with those of other opioids such as fentanyl and other related opioid agonists. Thus, it can be inferred that the abuse potential of these substances is similar to mu-opioid receptor agonists such as fentanyl and morphine.

6. *What, if Any, Risk There is to the Public Health:* Available evidence on the overall public health risks associated with cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl can be measured by hospitalization or fatalities associated with the use of such substances. Other countries have identified fatal and non-fatal intoxications from toxicological samples for *para*-methoxybutyryl fentanyl and *para*-chloroisobutyryl fentanyl. Abusers of these substances may not know the origin, identity, or purity of these substances, thus posing significant adverse health risks when compared to abuse of pharmaceutical

preparations of opioid analgesics, such as morphine and oxycodone. The abuse of cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl leads to the same qualitative public health risks as heroin, fentanyl and other opioid analgesic substances. Taken together, evidence posits that individuals experimenting with substances with unknown potency are at high risk of adverse health outcomes.

7. Its Psychic or Physiological Dependence Liability: There are no pre-clinical or clinical studies that have evaluated the psychic or physiologic dependence of cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl. Several studies have shown that due to fentanyl's short duration of action, more frequent dosing is often required that can lead to a fast induction of tolerance, dependence and opiate withdrawal syndrome. Opioid withdrawal includes nausea and vomiting, depression, agitation, anxiety, craving, sweats, hypertension, diarrhea, and fever. These five substances act as agonists at the mu-opioid receptors and exhibit a full and dose-dependent substitution for the discriminative stimulus effects produced by morphine. Thus, the pharmacological similarity and pattern of abuse of cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl to fentanyl are indicative of their potential to possess a psychic and physiological dependence liability similar to that of other mu-opioid receptor agonist substances, such as heroin and fentanyl.

8. Whether the Substance is an Immediate Precursor of a Substance Already Controlled Under the CSA: Cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl are not

immediate precursors of any controlled substance of the CSA as defined by 21 U.S.C. 802(23).

Conclusion: After considering the scientific and medical evaluation conducted by the HHS, the HHS's recommendation, and the DEA's own eight-factor analysis, the DEA finds that the facts and all relevant data constitute substantial evidence of the potential for abuse of cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl. As such, DEA hereby proposes to permanently schedule cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl as schedule I controlled substances under the CSA.

Proposed Determination of Appropriate Schedule

The CSA establishes five schedules of controlled substances known as schedules I, II, III, IV, and V. The CSA also outlines the findings required to place a drug or other substance in any particular schedule. (21 U.S.C. 812(b)). After consideration of the analysis and recommendation of the Assistant Secretary for HHS and review of all other available data, the Acting Administrator of the DEA, pursuant to 21 U.S.C. 811(a) and 21 U.S.C. 812(b)(1), finds that:

1. Cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl have a high potential for abuse as indicated either by law enforcement data, intoxications reported by scientific literature, or pharmacological testing of these substances;

2. Cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl have no currently accepted medical use in treatment in the United States;⁹ and
3. There is a lack of accepted safety for use of cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl under medical supervision.

Based on these findings, Acting Administrator of DEA concludes that cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl, including their isomers, esters, ethers, salts, and salts of isomers, esters and ethers whenever the existence of such isomers, esters, ethers and salts is possible, warrant continued control in schedule I of the CSA. (21 U.S.C. 812(b)(1)).

Requirements for Handling cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl

If this rule is finalized as proposed, cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl would

⁹ Although there is no evidence suggesting that cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl have a currently accepted medical use in treatment in the United States, it bears noting that a drug cannot be found to have such medical use unless DEA concludes that it satisfies a five-part test. Specifically, with respect to a drug that has not been approved by the FDA, to have a currently accepted medical use in treatment in the United States, all of the following must be demonstrated:

- i. the drug's chemistry must be known and reproducible;
- ii. there must be adequate safety studies;
- iii. there must be adequate and well-controlled studies proving efficacy;
- iv. the drug must be accepted by qualified experts; and
- v. the scientific evidence must be widely available.

continue¹⁰ to be subject to the CSA's schedule I regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, dispensing, importing, exporting, research, and conduct of instructional activities, including the following:

1. *Registration.* Any person who handles, manufactures, distributes, dispenses, imports, exports, engages in research, or conducts instructional activities or chemical analysis with, or possesses cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl, or who desires to handle cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl, is required to 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.

2. *Security.* Cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl are subject to schedule I security requirements and must be handled and stored pursuant to 21 U.S.C. 821, 823, and in accordance with 21 CFR 1301.71–1301.93.

3. *Labeling and Packaging.* All labels and labeling for commercial containers of cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl must be in compliance with 21 U.S.C. 825 and 958(e), and be in accordance with 21 CFR part 1302.

4. *Quota.* Only registered manufacturers are permitted to manufacture cyclopentyl

¹⁰ Cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl are currently subject to schedule I controls on a temporary basis, pursuant to 21 U.S.C. 811(h). 83 FR 4580, February 1, 2018.

fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl in accordance with a quota assigned pursuant to 21 U.S.C. 826 and in accordance with 21 CFR part 1303.

5. *Inventory.* Any person registered with DEA to handle cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl must have an initial inventory of all stocks of controlled substances including these substances 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 cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl) 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.

6. *Records and Reports.* Every DEA registrant is required to maintain records and submit reports with respect to cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl, pursuant to 21 U.S.C. 827 and 958(e), and in accordance with 21 CFR parts 1304 and 1312.

7. *Order Forms.* Every DEA registrant who distributes cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl is required to comply with the order form requirements, pursuant to 21 U.S.C. 828, and 21 CFR part 1305.

8. *Importation and Exportation.* All importation and exportation of cyclopentyl

fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl must be in compliance with 21 U.S.C. 952, 953, 957, and 958, and in accordance with 21 CFR part 1312.

9. *Liability.* Any activity involving cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl not authorized by, or in violation of, the CSA or its implementing regulations is unlawful, and could subject the person to administrative, civil, and/or criminal sanctions.

Regulatory Analyses

Executive Orders 12866, 13563, and 13771, Regulatory Planning and Review, Improving Regulation and Regulatory Review, and Reducing Regulation and Controlling Regulatory Costs

In accordance with 21 U.S.C. 811(a), this proposed scheduling action is subject to formal rulemaking procedures 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 proposed rule does not meet the definition of an Executive Order 13771 regulatory action, and the repeal and cost offset requirements of Executive Order 13771 have not been triggered. OMB has previously determined that formal rulemaking actions concerning the scheduling of controlled substances, such as this rule, are not significant regulatory actions under Section 3(f) of Executive Order 12866.

Executive Order 12988, Civil Justice Reform

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

Executive Order 13132, Federalism

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

Executive Order 13175, Consultation and Coordination with Indian Tribal Governments

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

Regulatory Flexibility Act

The Administrator, in accordance with the Regulatory Flexibility Act (RFA), 5 U.S.C. 601–602, has reviewed this proposed rule and by approving it, certifies that it will not have a significant economic impact on a substantial number of small entities. On February 1, 2018, the DEA published an order to temporarily place cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl in schedule I of the CSA pursuant to the temporary scheduling provisions

of 21 U.S.C. 811(h). DEA estimates that all entities handling or planning to handle cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, and valeryl fentanyl have already established and implemented the systems and processes required to handle these substances.

There are currently 34 registrations authorized to handle one or more of the following substances: cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, or valeryl fentanyl, as well as a number of registered analytical labs that are authorized to handle schedule I controlled substances generally. These 34 registrations represent 26 entities, of which 8 are small entities. Therefore, DEA estimates 8 small entities are affected by this proposed rule. A review of the 34 registrations indicates that all entities that currently handle cyclopentyl fentanyl, isobutyryl fentanyl, *para*-chloroisobutyryl fentanyl, *para*-methoxybutyryl fentanyl, or valeryl fentanyl also handle other schedule I controlled substances and have established and implemented (or maintain) the systems and processes required to handle these substances. Therefore, the DEA anticipates that this proposed rule will impose minimal or no economic impact on any affected entities; and thus, will not have a significant economic impact on any of the eight affected small entities. Therefore, DEA has concluded that this proposed rule will not 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.*, 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 annually for inflation) in any 1 year. . . .” Therefore, neither a Small Government Agency Plan nor any other action is required under UMRA of 1995.

Paperwork Reduction Act of 1995

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

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, drug traffic control, reporting and recordkeeping requirements.

For the reasons set out above, DEA proposes to amend 21 CFR part 1308 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 § 1308.11:

- a. Redesignate paragraphs (b)(56) through (70) as (b)(60) through (74);
- b. Redesignate paragraphs (b)(54) and (55) as (b)(57) and (58);
- c. Redesignate paragraphs (b)(39) through (53) as (b)(41) through (55);
- d. Redesignate paragraphs (b)(22) through (38) as (b)(23) through (39);
- e. Add new paragraphs (b)(22), (40), (56), (59), and (75); and

f. Remove and reserve paragraphs (h)(23), and (h)(25) through (28).

The additions read as follows:

§ 1308.11 Schedule I.

* * * * *

(b) * * *

(22) Cyclopentyl fentanyl (*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylcyclopentanecarboxamide)

.....(9847)

* * * * *

(40) Isobutyryl fentanyl (*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylisobutyramide)

.....(9827)

* * * * *

(56) *para*-Chloroisobutyryl fentanyl (*N*-(4-chlorophenyl)-*N*-(1-phenethylpiperidin-4-yl)isobutyramide).....(9826)

* * * * *

(59) *para*-Methoxybutyryl fentanyl (*N*-(4-methoxyphenyl)-*N*-(1-phenethylpiperidin-4-yl)butyramide)(9837)

* * * * *

(75) Valeryl fentanyl (*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylpentanamide)
.....(9804)

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Dated: January 23, 2020.

Uttam Dhillon,
Acting Administrator.

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