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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-1457]

Schedules of Controlled Substances: Placement of Seven Specific Fentanyl-Related Substances in Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Drug Enforcement Administration proposes placing seven fentanyl-related substances, as identified in this proposed rule, in schedule I of the Controlled Substances Act. These seven substances fall within the definition of fentanyl-related substances set forth in the February 6, 2018 temporary scheduling order. Through the Temporary Reauthorization and Study of Emergency Scheduling of Fentanyl Analogues Act, which became law on February 6, 2020, Congress extended the temporary control of fentanyl-related substances until May 6, 2021. This temporary order was subsequently extended multiple times, most recently on December 29, 2022, through the Consolidated Appropriations Act, 2023, which extended the order until December 31, 2024. 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 these seven specific controlled substances.

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 a hearing or waiver of hearing pursuant to 21 CFR 1308.44 and in accordance with 21 CFR 1316.47 and/or 1316.49, as applicable. Requests

for a 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). To ensure proper handling of comments, please reference "Docket No. DEA-1457" on all electronic and written correspondence, including any attachments.

- *Electronic comments:* The Drug Enforcement Administration (DEA) encourages commenters to submit all comments 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 *https://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. 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. 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.

- *Paper comments:* Paper comments that duplicate electronic submissions 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/DPW, 8701 Morrissette Drive, Springfield, Virginia 22152.

- *Hearing requests:* All requests for a hearing and waivers of participation, together with a written statement of position on the matters of fact and law asserted in the hearing, must be filed with the DEA Administrator, who will make the determination of whether a hearing will be needed to address such matters of fact and law in the rulemaking. Such requests must be sent to: Drug Enforcement Administration, Attn: Administrator, 8701

Morrissette Drive, Springfield, Virginia 22152. For informational purposes, a courtesy copy of requests for hearing and waivers of participation should also be sent to: (1) Drug Enforcement Administration, Attn: Hearing Clerk/OALJ, 8701 Morrissette Drive, Springfield, Virginia 22152; and (2) Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrissette Drive, Springfield, Virginia 22152.

- *Paperwork Reduction Act Comments*: All comments concerning collections of information under the Paperwork Reduction Act must be submitted to the Office of Information and Regulatory Affairs, OMB, Attention: Desk Officer for DOJ, Washington, DC 20503. Please state that your comment refers to Docket No. DEA-1457.

FOR FURTHER INFORMATION CONTACT: Dr. Terrence L. Boos, Drug and Chemical Evaluation Section, Diversion Control Division, Drug Enforcement Administration; Telephone: (571) 362-3249.

SUPPLEMENTARY INFORMATION: In this proposed rule, the Drug Enforcement Administration (DEA) proposes to permanently schedule the following seven controlled substances in schedule I of the Controlled Substances Act (CSA), 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 within the specific chemical designation:

- *para*-chlorofentanyl (*N*-(4-chlorophenyl)-*N*-(1-phenethylpiperidin-4-yl)propionamide),
- *ortho*-chlorofentanyl (*N*-(2-chlorophenyl)-*N*-(1-phenethylpiperidin-4-yl)propionamide),
- *meta*-fluorofuranyl fentanyl (*N*-(3-fluorophenyl)-*N*-(1-phenethylpiperidin-4-yl)furan-2-carboxamide),
- *ortho*-methylcyclopropyl fentanyl (*N*-(2-methylphenyl)-*N*-(1-phenethylpiperidin-4-yl)cyclopropanecarboxamide),

- *beta*-methylacetyl fentanyl (*N*-phenyl-*N*-(1-(2-phenylpropyl)piperidin-4-yl)acetamide),
- tetrahydrothiofuranyl fentanyl (*N*-(1-phenethylpiperidin-4-yl)-*N*-phenyltetrahydrothiophene-2-carboxamide),
- *para*-fluoro valeryl fentanyl (*N*-(4-fluorophenyl)-*N*-(1-phenethylpiperidin-4-yl)pentanamide).

Posting of Public Comments

All comments received in response to this docket are considered part of the public record. DEA will make comments available for public inspection online at *https://www.regulations.gov*, unless reasonable cause is given. Such information includes personal or business identifiers (such as name, address, state of federal identifiers, etc.) voluntarily submitted by the commenter.

Commenters submitting comments which include personal identifying information (PII), confidential, or proprietary business information that the commenter does not want made publicly available should submit two copies of the comment. One copy must be marked "CONTAINS CONFIDENTIAL INFORMATION" and should clearly identify all PII or business information the commenter does not want to be made publicly available, including any supplemental materials. DEA will review this copy, including the claimed PII and confidential business information, in its consideration of comments. The second copy should be marked "TO BE PUBLICLY POSTED" and must have all claimed confidential PII and business information already redacted. DEA will post only the redacted comment on *https://www.regulations.gov* for public inspection. DEA generally will not redact additional information contained in the comment marked "TO BE PUBLICLY POSTED." The Freedom of Information Act applies to all comments received.

For easy reference, an electronic copy of this document and supplemental information to this proposed scheduling action are available at *https://www.regulations.gov*.

Request for Hearing or Appearance; Waiver

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.[1] Interested persons, as defined in 21 CFR 1300.01(b), may file requests for a hearing in conformity with the requirements of 21 CFR 1308.44(a) and 1316.47(a), and such requests must:

(1) state with particularity the interest of the person in the proceeding;

(2) state with particularity the objections or issues concerning which the person desires to be heard; and

(3) state briefly the position of the person with regard to the objections or issues.

Any interested person may file a waiver of an opportunity for a hearing or to participate in a hearing in conformity with the requirements of 21 CFR 1308.44(c), together with a written statement of position on the matters of fact and law involved in any hearing.[2]

All requests for a hearing and waivers of participation, together with a written statement of position on the matters of fact and law involved in such hearing, must be sent to DEA using the address information provided above. The decision whether a hearing will be needed to address such matters of fact and law in the rulemaking will be made by the Administrator. If a hearing is needed, DEA will publish a notification of hearing on the proposed rulemaking in the *Federal Register*.[3] Further, once the Administrator determines a hearing is needed to address such matters of fact and law in rulemaking, she will then designate an Administrative Law Judge (ALJ) to preside over the hearing. The ALJ's functions shall only commence upon designation, as provided in 21 CFR 1316.52.

In accordance with 21 U.S.C. 811 and 812, the purpose of a hearing would be to determine whether *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl,

[1] 21 CFR 1308.41 through 1308.45; 21 CFR part 1316, subpart D.
[2] 21 CFR 1316.49.
[3] 21 CFR 1308.44(b), 1316.53.

and *para*-fluoro valeryl fentanyl meet the statutory criteria for placement in schedule I, as proposed in this rule.

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 (delegated to the Administrator of DEA pursuant to 28 CFR 0.100) on his own motion, at the request of the Secretary of Health and Human Services (HHS), or on the petition of an interested party.[4] This proposed action is initiated on the Administrator's own motion and supported by, *inter alia*, a recommendation from the Assistant Secretary for Health of HHS (Assistant Secretary for HHS or Assistant Secretary) and an evaluation of all other relevant data by DEA. If finalized, this action would make permanent the existing temporary regulatory controls and administrative, civil, and criminal sanctions of schedule I controlled substances on any person who handles or proposes to handle these seven substances.

Background

On February 6, 2018, pursuant to 21 U.S.C. 811(h)(1), DEA published an order in the *Federal Register* (83 FR 5188) temporarily placing fentanyl-related substances, as defined in that order, in schedule I of the CSA based upon a finding that these substances pose an imminent hazard to the public safety.[5] As discussed below in Factor 3, the seven substances named in this proposed rule meet the existing definition of fentanyl-related substances as they are not otherwise controlled in any other schedule (i.e., not included under another DEA Controlled Substance Code Number) and are structurally related to fentanyl by one or more of the five modifications listed under the definition. That temporary order was effective upon the date of publication. Pursuant to 21 U.S.C. 811(h)(2), the temporary control of fentanyl-related substances, a class of substances as defined in the order, as well as the seven specific substances

[4] 21 U.S.C. 811(a).
[5] *Schedules of Controlled Substances: Temporary Placement of Fentanyl-Related Substances in Schedule I*, 83 FR 5188 (Feb. 6, 2018).

already covered by that order, was set to expire on February 6, 2020. However, on February 6, 2020, as explained in DEA's April 10, 2020 correcting amendment[6]), Congress extended that expiration date until May 6, 2021, by enacting the Temporary Reauthorization and Study of the Emergency Scheduling of Fentanyl Analogues Act.[7] This temporary order was subsequently extended multiple times, most recently on December 29, 2022, through the Consolidated Appropriations Act, 2023,[8] which extended the order until December 31, 2024. Consequently, the temporary control of these seven substances will remain in effect until December 31, 2024, unless it is extended. Accordingly, as published elsewhere in this issue of the *Federal Register*, the DEA Administrator is ordering an extension of this temporary order as it relates to these seven substances.

The Administrator, on her own motion pursuant to 21 U.S.C. 811(a), is initiating proceedings to permanently schedule *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl*, beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl in schedule I of the CSA. Pursuant to 21 U.S.C. 811(b), DEA gathered the necessary data 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 April 3, 2023, in accordance with 21 U.S.C. 811(b), the 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 these seven substances.

On October 25, 2024, the Assistant Secretary submitted HHS's scientific and medical evaluation and scheduling recommendation for *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl*, beta*-methylacetyl fentanyl,

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[6] *Schedules of Controlled Substances: Temporary Placement of Fentanyl-Related Substances in Schedule I; Correction***,** 85 FR 20155 (Apr. 10, 2020).
[7] Pub. L. 116-114, sec. 2, 134 Stat. 103.
[8] Pub. L. 117-328, division O, title VI, sec. 601.

tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl and their salts to the Administrator. The Secretary recommended placing these seven fentanyl related substances in schedule I of the CSA. In accordance with 21 U.S.C. 811(c), upon receipt of the scientific and medical evaluation and scheduling recommendation from HHS, DEA reviewed the documents and all other relevant data and conducted its own eight-factor analysis of the abuse potential of these seven substances.

Proposed Determination to Permanently Schedule Seven Specific Fentanyl-Related Substances

As discussed in the background section, the Administrator is initiating proceedings, pursuant to 21 U.S.C. 811(a), to permanently add *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl to schedule I. DEA 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 seven substances pursuant to 21 U.S.C. 811(c). Included below is a brief summary of each factor as analyzed by HHS and DEA, and as considered by DEA in its proposed scheduling action. Readers should refer to the full eight-factor analyses prepared by HHS and by DEA in support of this proposal, which are available in their entirety under "Supporting Documents" of the public docket for this proposed rule at *https://www.regulations.gov* under Docket Number "DEA-1457."

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

In addition to considering the information HHS provided in its scientific and medical evaluation document for these seven fentanyl-related substances, DEA also considered all other relevant data regarding actual or relative potential for abuse of these three substances. The term "abuse" is not defined in the CSA; however, the legislative history of the CSA suggests that

DEA consider the following criteria when determining whether a particular drug or substance has a potential for abuse: [9]

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.

Law enforcement seizure data indicate that individuals have and are using *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl 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, especially since there is no currently accepted medical use for these seven substances. According to the National Forensic Laboratory Information System (NFLIS-Drug)[10] database, which collects drug identification results from drug cases submitted to and analyzed by Federal, State, and local forensic laboratories, there have been 214 reports for *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl between 2020 and 2024. According to HHS, *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-

[9] 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.

[10] The National Forensic Laboratory Information System (NFLIS) represents an important resource in monitoring illicit drug 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 more than 96% 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 Schedules of Controlled Substances: Placement of Carisoprodol Into Schedule IV*, 76 FR 77330, 77332 (Dec. 12, 2011). NFLIS data were queried November 1, 2024.

fluorofuranyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl are not legally marketed as drugs in the United States or anywhere else in the world. These substances have no approved medical use other than their limited use in scientific research. As such, the legal sources of the substances are limited to legitimate chemical companies supplying them for scientific research.

para-Chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl are not approved for medical use and are not formulated or approved for clinical use. As such, all use is on an individual's own initiative, rather than on the basis of medical advice from a practitioner licensed by law to administer drugs. Law enforcement seizures and case reports demonstrate that individuals are taking these seven fentanyl-related substances on their own initiative, rather than on the basis of medical advice from a licensed practitioner.

Based on available data, *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl, are related in their effects to the actions of other mu-opioid receptor (MOR) agonists,[11] such as fentanyl, that are already listed as having potential for abuse. Because high doses of MOR agonists can produce respiratory depression leading to death, these fentanyl-related substances at high doses have substantial capability of creating hazards to the health of the user or to the safety of the community. According to HHS, these seven fentanyl-related substances exert their actions at least in part through the MOR and thus have a high likelihood of having substantially similar potential for abuse as other schedule I opioids. Both DEA's and HHS's eight-factor analyses found that the abuse potential of these

[11] Drug Enforcement Administration–Veterans Affairs (DEA-VA) Interagency Agreement. Binding and Functional Activity at Delta, Kappa and Mu Opioid Receptors. In Vitro Receptor and Transporter Assays for Abuse Liability Testing for the DEA by the VA (unpublished data).

substances is similar to other schedule I opioids and presents a hazard to the health and safety of individuals and the community.

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

According to DEA and HHS, the pharmacological activity of these substances in humans is unknown. Data obtained from preclinical studies show that these fentanyl-related substances (*para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl) exhibit a pharmacological profile similar to that of fentanyl, morphine, and several schedule I opioid substances that are structurally related to fentanyl. Similar to fentanyl and other structurally related synthetic opioids, fentanyl-related substances namely *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl have been shown to bind to the mu-opioid receptors with varying affinities.[12] Also, similar to fentanyl and other structurally related synthetic opioids, these seven fentanyl-related substances behave as agonists at the MOR sites in *in vitro* functional studies.

Studies conducted to examine the antinociceptive effect of the seven fentanyl-related substances in a warm water tail-withdrawal assay and their mediation by opioid receptors as determined by naltrexone antagonism showed these seven fentanyl-related substances, similar to fentanyl and morphine, produced antinociceptive effects as measured by an increase in tail withdrawal latency.[13] Pre-treatment with naltrexone, an opioid receptor antagonist, attenuated antinociceptive effects of the seven-fentanyl related substance*s*. These data demonstrate that similar to morphine and fentanyl, *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl

[12] *in vitro* Pharmacology data was collected through DEA—Veterans Affairs interagency agreement: "*in vitro* Receptor and Transporter Assays for Abuse Liability Testing for the DEA by the VA".
[13] Gatch MB. (2024). Test of analgesic effects alone and in combination with naltrexone. 15DDHQ19F00001173, "Evaluation of Abuse Potential of Synthetic Opioids Using in Vivo Pharmacological Studies" (unpublished data).

fentanyl, *para*-fluoro valeryl fentanyl produced dose-dependent antinociception in the warm-water tail-withdrawal assay that can be attenuated by naltrexone pre-treatment.

There is a strong correlation between the discriminative stimulus effects of a given drug in animals and its subjective effects in humans.[14] Data from drug discrimination studies[15] show that the seven-fentanyl related substances fully and dose-dependently substitute for the discriminative stimulus effects produced by morphine in Sprague Dawley rats trained to discriminate 3.2 mg/kg morphine from saline.[16] These data demonstrate *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl, similar to morphine (schedule II) and fentanyl (schedule II), are mu-opioid receptor agonists.

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

para-Chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl are synthetic opioids in the 4-anilidopiperidine structural class which includes fentanyl. As defined in the February 6, 2018 temporary scheduling order, fentanyl-related substances include any substance not otherwise controlled in any schedule (*i.e.*, not included under any other Administration Controlled Substance Code Number) that is structurally related to fentanyl by one or more of the following modifications:

(A) Replacement of the phenyl portion of the phenethyl group by any monocycle, whether or not further substituted in or on the monocycle;

(B) substitution in or on the phenethyl group with alkyl, alkenyl, alkoxyl, hydroxyl, halo, haloalkyl, amino or nitro groups;

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[14] Solinas M, Panlilio LV, Justinova Z, Yasar S, Goldberg SR. (2006). Using drug-discrimination techniques to study the abuse-related effects of psychoactive drugs in rats. Nat Protoc.1(3):1194-206.

[15] Drug discrimination is widely used to determine whether a new test drug or substance is pharmacologically similar to a known drug of abuse.

[16] DEA–Synthetic Opioids Purchase Agreement (2022-2024). Evaluation of synthetic opioid substances using analgesia and the drug discrimination assay. In Vivo Testing for the DEA by Gatch (Univ. of North Texas).

(C) substitution in or on the piperidine ring with alkyl, alkenyl, alkoxyl, ester, ether, hydroxyl, halo, haloalkyl, amino or nitro groups;

(D) replacement of the aniline ring with any aromatic monocycle, whether or not further substituted in or on the aromatic monocycle; and/or

(E) replacement of the *N*-propionyl group by another acyl group.

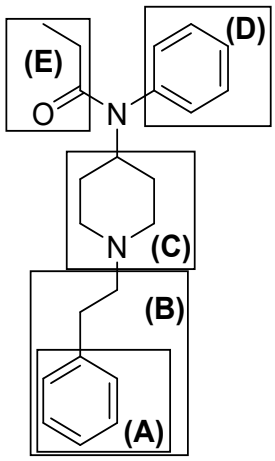

Figure 1: Regions of the chemical structure of fentanyl described in the definition of a fentanyl-related substance

According to the February 6, 2018 temporary scheduling order, the existence of a substance with anyone, or any combination, of above-mentioned modifications (see figure 1) would meet the structural requirements of the definition of fentanyl-related substances. The present seven substances fall within the definition of fentanyl-related substances by the following modifications:

1. *para*-chlorofentanyl: substitution on the aniline ring (meets definition for modification D);
2. *ortho*-chlorofentanyl: substitution on the aniline ring (meets definition for modification D);
3. *meta*-fluorofuranyl fentanyl: substitution on the aniline ring and replacement of the *N*-propionyl group with another acyl group (meets definition for modifications D and E);

4. *ortho*-methylcyclopropyl fentanyl: substitution on the aniline ring and replacement of the *N*-propionyl group with another acyl group (meets definition for modifications D and E);

5. *beta*-methylacetyl fentanyl: substitution on the phenethyl group with an alkyl group and replacement of the *N*-propionyl group with another acyl group (meets definition for modifications B and E);

6. tetrahydrothiofuranyl fentanyl: replacement of the *N*-propionyl group with another acyl group (meets definition for modification E);

7. *para*-fluoro valeryl fentanyl: substitution on the aniline ring and replacement of the *N*-propionyl group with another acyl group (meets definition for modifications D and E).

4. *Its History and Current Pattern of Abuse*

Evidence suggests that the pattern of abuse of *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl parallels that of prescription opioid analgesics. Currently, the United States is in the midst of an illicit opioid abuse epidemic. There has been a marked increase in the encounters of synthetic opioids that are structurally related to fentanyl that parallels an increase in deaths related to synthetic opioids. Thus, the recreational abuse of fentanyl-like substances continues to be a significant concern. These substances are distributed to users, often with unpredictable outcomes. *para*-Chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl have been encountered by law enforcement officials.

Law enforcement encountered these seven substances in the United States. According to the NFLIS[17] database, 214 reports were registered containing six of the substances (*para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl) from state or local forensic laboratories from 2020 to 2024. *ortho*-Methylcyclopropyl fentanyl was not specifically listed in the NFLIS database, although in 2018, there were three reports of methylcyclopropyl fentanyl.

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

The rapid appearance of fentanyl-related substances presents numerous challenges for forensic and toxicology laboratories. The identification of a new substance requires full structural elucidation, sometimes requiring specialized instrumentation not available to all forensic laboratories. Laboratories are required to quickly adapt testing procedures to identify new substances. It remains likely that the prevalence of these substances in opioid related emergency room admissions and deaths is underreported as standard immunoassays may not differentiate fentanyl from substances structurally related to fentanyl.

The population likely to abuse fentanyl-related substances overlaps with the population abusing prescription opioid analgesics, heroin, fentanyl, and other synthetic opioid substances. Because abusers of fentanyl-related substances are likely to obtain these substances through unregulated sources, the identity, purity, and quantity are uncertain and inconsistent, thus posing significant adverse health risks to the end user. The misuse and abuse of opioids have been demonstrated and are well characterized. According to the most recent data from the National Survey on Drug Use and Health (NSDUH)[18] of the Substance Abuse and Mental Health Services

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[17] NFLIS data were queried November 1, 2024. NFLIS data reporting is still pending for 2023 and 2024 due to normal lag time.

[18] 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 Services 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.

Administration (SAMHSA),[19] in 2023, an estimated 8.9 million people aged 12 or older misused opioids in the past year, including 8.6 million prescription pain reliever misusers and 660,000 heroin users. In 2023, among people aged 12 or older, 828,000 people misused fentanyl in the past year. NSDUH data show that among people aged 12 or older in 2023, 627,000 people used illicitly manufactured fentanyl in the past year. This population is likely to be at risk of abusing fentanyl-related substances. Individuals who initiate (i.e., use a drug for the first time) use of fentanyl-related substances are likely to be at risk of developing substance use disorder, overdose, and death, similar to the risks of other opioid analgesics (e.g., fentanyl, morphine, etc.).

According to HHS, it is highly likely that the prevalence of these fentanyl-related substances in emergency room admissions and fatalities is under reported because standard immunoassays may not be sufficient to distinguish between fentanyl and substances that are structurally related to fentanyl. Law enforcement reports demonstrate *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl are being illicitly distributed and abused. The use of these seven fentanyl-related substances is likely to increase the scope, duration, and significance of abuse based on their pharmacological similarity to drugs that are abused in the current opioid epidemic (e.g., fentanyl).

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

The increase in opioid overdose deaths in the United States has been exacerbated by the availability of potent synthetic opioids such as fentanyl and numerous other structurally related substances in the illicit drug market.[20] These substances have a history of being trafficked as

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[19] The Substance Abuse and Mental Health Services Administration (SAMHSA) is a branch of the U.S. Department of Health and Human Services (HHS). It is charged with improving the quality and availability of prevention, treatment, and rehabilitative services in order to reduce illness, death disability, and cost to society resulting from substance abuse and mental illness.

[20] Centers for Disease Control and Prevention, (2024, April). Understanding the opioid overdose epidemic. https://www.cdc.gov/ overdose-prevention/about/understanding-the-opioid-overdose epidemic.html Spencer, M. R., Warner, M., Cisewski, J. A., Miniño, A., Dodds, D., Perera, J., & Ahmad, F. B., Estimates of drug overdose deaths involving fentanyl, methamphetamine, cocaine, heroin, and oxycodone: United States, 2021. Vital Statistics Rapid

replacements for other opioids, such as heroin and other synthetic opioids. Fentanyl is a potent synthetic opioid that is primarily prescribed for acute and chronic pain and is approximately 100 times more potent than morphine. As such, fentanyl has a high risk of abuse, dependence and overdose that can lead to death. Because fentanyl-related substances have a similar chemical structure to fentanyl, these substances are expected to have similar biological effects. Indeed, these seven fentanyl-related substances produced pharmacological effects similar to fentanyl. The adverse effects of substances structurally related to fentanyl on humans are largely identical to those of fentanyl and other opioid analgesics. These fentanyl-related substances pose the same qualitative public health risks as heroin, fentanyl, and other opioid analgesic substances. The DEA Toxicology Testing Program (DEA-Tox)[21] identified three drug paraphernalia where *para*-chlorofentanyl was detected. These cases occurred between May 2022 and June 2024. As the data demonstrate, the potential for overdoses exists for these substances and these substances pose risk to public health.

According to HHS, the lack of hospitalization or fatality for these seven fentanyl-related substances is not surprising because the enzyme linked immunosorbent assay (ELISA) which is used to detect fentanyl cross-reacts with fentanyl-related substances when fentanyl is present above a threshold level.[22] Thus, fatalities that might be associated with the fentanyl-related substances may be underreported. As with any opioid not approved for medical use, the health and safety risks for users are high. Public health data suggest that *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl may be a direct risk to public health.

Release (Report No. 27). National Center for Health Statistics; Zibbell, J. E., Aldridge, A., Grabenauer, M., Heller, D., Duhart Clarke, S., Pressley, D., & Smiley-McDonald, H. (2023). Associations between opioid overdose deaths and drugs confiscated by law enforcement and submitted to crime laboratories for analysis, United States, 2014–2019: An observational study. The Lancet Regional Health–Americas, 25.

[21] DEA-TOX is a DEA-run program whereby unused biological samples from victims of drug overdoses can be extensively tested for the presence of novel psychoactive substances, in addition to other drugs of abuse.

[22] Guerrieri D, Kjellqvist F, Kronstrand R, Gréen H. (2019). Validation and Cross-Reactivity Data for Fentanyl Analogs with the Immunalysis Fentanyl ELISA. J Anal Toxicol. 43(1):18-24.

7. *Its Psychic or Physiological Dependence Liability*

According to HHS, the psychic or physiologic dependence of these seven fentanyl-related substances has not been studied in clinical studies and is therefore unknown. HHS notes that pharmacology data for these substances as MOR agonists with known abuse potential demonstrates their property of producing physical and psychic dependence similar to other MOR agonists. The discontinuation of the use of MOR agonists, such as morphine and fentanyl (Schedule II drugs), is associated with withdrawal symptoms indicative of physical dependence. Opioid withdrawal syndrome is characterized by central nervous system irritability, gastrointestinal dysfunction, yawning, diaphoresis, and fever.[23] Thus, the pharmacological similarity and pattern of abuse of *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl 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*

para-Chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl are not immediate precursors of any controlled substance of the CSA, as defined by 21 U.S.C. 802(23).

Conclusion: Based on consideration of the scientific and medical evaluation and accompanying recommendation of HHS, and on DEA's own eight-factor analysis, DEA finds that these facts and all relevant data constitute substantial evidence of potential for abuse of *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-

[23] Katz R, Kelly W, Hsi A. (1994). Prospective-study on the occurrence of withdrawal in critically ill children who receive fentanyl by continuous-infusion. Critical Care Medicine 16:763–767.

methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl. As such, DEA proposes to permanently schedule these seven substances as 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.[24] After consideration of the analysis and recommendation of the Assistant Secretary for HHS and review of all other available data, the Administrator of DEA, pursuant to 21 U.S.C. 811(a) and 812(b)(1), finds that:

(1) *para*-Chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl, similar to fentanyl, are mu-opioid receptor agonists. The seven fentanyl-related substances have analgesic effects, and these effects are mediated by μ-opioid receptor agonism. These substances that produce mu-opioid receptor agonist effects in the CNS are considered as having a high potential for abuse (e.g. morphine and fentanyl). Data obtained from drug discrimination studies indicate that *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl fully substituted for the discriminative stimulus effects of morphine. Thus, these substances have a high potential for abuse.

(2) There is no FDA-approved drug application for *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl in the United States. Further, there are no adequate and well-controlled clinical studies for any of these substances, and there are no well-defined finished dosage forms for any of these fentanyl-related

[24] *See* 21 U.S.C. 812(b).

substances. There are no known therapeutic applications for these seven fentanyl-related substances, and thus they have no currently accepted medical use in the United States.[25]

(3) There is a lack of accepted safety for use of *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl under medical supervision. Because these seven substances have no FDA-approved medical use and have not been investigated as new drugs, their safety for use under medical supervision has not been determined. Therefore, there is a lack of accepted safety for use of these seven substances under medical supervision.

Based on these findings, the Administrator of DEA concludes that *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro 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 within the specific chemical designation, warrant continued control in schedule I of the CSA.[26]

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[25] Pursuant to 21 U.S.C 812(b)(1)(B), when placing a drug or substance in schedule I of the CSA, DEA must consider whether the substance has a currently accepted medical use in treatment in the United States. First, DEA looks to whether the drug or substance has FDA approval. When no FDA approval exists, DEA has traditionally applied a five-part test to a drug or substance to determine whether a drug or substance has a currently medical use: 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. Marijuana Scheduling Petition; Denial of Petition; Remand, 57 FR 10499 (Mar. 26, 1992), *pet. for rev. denied, Alliance for Cannabis Therapeutics v. Drug Enforcement Admin.*, 15 F.3d 1131, 1135 (D.C. Cir. 1994). DEA applied the traditional five-part test and concluded the test was not satisfied. In a recent published letter in a different context, HHS applied an additional two-part test to determine currently accepted medical use for substances that do not satisfy the five-part test: (1) whether there exists widespread, current experience with medical use of the substance by licensed health care providers operating in accordance with implemented jurisdiction-authorized programs, where medical use is recognized by entities that regulate the practice of medicine, and, if so, (2) whether there exists some credible scientific support for at least one of the medical conditions for which part (1) is satisfied. On April 11, 2024, the Department of Justice's Office of Legal Counsel (OLC) issued an opinion, which, among other things, concluded that HHS's two-part test would be sufficient to establish that a drug has a currently accepted medical use. Office of Legal Counsel, Memorandum for Merrick B. Garland Attorney General Re: Questions Related to the Potential Rescheduling of Marijuana at 3 (April 11, 2024). In its eight-factor assessment, HHS determined that these seven fentanyl-related substances did not satisfy this two-part test. Therefore, since both DEA and HHS have determined that these seven fentanyl-related substances do not satisfy the five-part test, and HHS has determined that these seven fentanyl-related substances do not satisfy the additional two-part test, DEA concludes that *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl do not have a currently accepted medical use.

[26] 21 U.S.C. 812(b)(1).

Requirements for Handling *para*-Chlorofentanyl, *ortho*-Chlorofentanyl, *meta*-Fluorofuranyl fentanyl, *ortho*-Methylcyclopropyl fentanyl, *beta*-Methylacetyl fentanyl, Tetrahydrothiofuranyl fentanyl, and *para*-Fluoro valeryl fentanyl

As discussed above, these seven fentanyl-related substances are currently subject to a temporary scheduling order, which added them to schedule I. If this rule is finalized as proposed, *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl would be subject, on a permanent basis, 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) *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl must be registered with 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.* *para*-Chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro 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 through 1301.76. Non-practitioners handling these seven substances also must comply with the screening requirements of 21 CFR 1301.90 through 1301.93.

3. *Labeling and Packaging.* All labels and labeling for commercial containers of *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and

para-fluoro valeryl fentanyl must comply 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 *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl*, beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro 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 *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl*, beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro 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 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 *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl*, beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl) on hand every two years pursuant to 21 U.S.C. 827 and 958(e) and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11.

6. *Records and Reports.* Every DEA registrant must maintain records and submit reports with respect to *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl*, beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl, pursuant to 21 U.S.C. 827, 832(a), and 958(e), and in accordance with 21 CFR 1301.74(b) and (c) and 1301.76(b) and parts 1304, 1312, and 1317. Manufacturers and distributors would be required to submit reports regarding *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl*, beta*-

methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl to the Automation of Reports and Consolidated Order System pursuant 21 U.S.C. 827, and in accordance with 21 CFR parts 1304 and 1312.

7. Order Forms. Every DEA registrant who distributes *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl*, beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl must 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 *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl*, beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro 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 *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl*, beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl 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

Executive Orders 12866, 13563, and 14094 (Regulatory Review)

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 (E.O.) 12866 and the principles reaffirmed in E.O. 13563. E.O. 14094 modernizes the regulatory review process to advance policies that promote the public interest and address national priorities.

Executive Order 12988, Civil Justice Reform

This proposed regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of E.O. 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 E.O. 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 E.O. 13175. It does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal Government and Indian tribes, or on the distribution of power and responsibilities between the Federal Government and Indian tribes.

Regulatory Flexibility Act

The Administrator, in accordance with the Regulatory Flexibility Act, 5 U.S.C. 601-612, has reviewed this rule and by approving it, certifies that it will not have a significant economic impact on a substantial number of small entities. On February 6, 2018, DEA published an order to temporarily place fentanyl-related substances, as defined in the order, in schedule I of the CSA pursuant to the temporary scheduling provisions of 21 U.S.C. 811(h). However, as explained in DEA's April 10, 2020 correcting amendment,[27] Congress extended that expiration date until May 6, 2021, by enacting the Temporary Reauthorization and Study of the Emergency Scheduling of Fentanyl Analogues Act.[28] This temporary order was subsequently extended multiple times,

[27] *Schedules of Controlled Substances: Temporary Placement of Fentanyl-Related Substances in Schedule I; Correction*, 85 FR 20155 (Apr. 10, 2020).
[28] Pub. L. 116-114, sec. 2, 134 Stat. 103.

most recently on December 29, 2022, through the Consolidated Appropriations Act, 2023,[29] which extended the order until December 31, 2024. DEA estimates that all entities handling or planning to handle *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl have already established and implemented systems and processes required to handle these substances which meet the definition of fentanyl-related substances.

There are currently 170 registrations authorized to specifically handle the fentanyl-related substances as a class, which include one or more of the following substances: *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl, as well as a number of registered analytical labs that are authorized to handle schedule I controlled substances generally. Some of these entities are likely to be large entities. However, since DEA does not have information of registrant size, DEA conservatively assumes all of 170 registrants affected by this rule are small entities.

A review of the 170 registrations indicates that all entities that currently handle *para*-chlorofentanyl, *ortho*-chlorofentanyl, *meta*-fluorofuranyl fentanyl, *ortho*-methylcyclopropyl fentanyl, *beta*-methylacetyl fentanyl, tetrahydrothiofuranyl fentanyl, and *para*-fluoro valeryl fentanyl also handle other schedule I controlled substances and have established and implemented (or maintained) systems and processes required to handle these substances. Therefore, 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 95 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

[29] Pub. L. 117-328, division O, title VI, sec. 601.

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 the UMRA of 1995.

Paperwork Reduction Act of 1995

This proposed rule would not impose a new collection or modify an existing collection of information under the Paperwork Reduction Act of 1995.[30] Also, this proposed rule would not impose new or modify existing recordkeeping or reporting requirements on state or local governments, individuals, businesses, or organizations. However, this proposed rule would require compliance with the following existing OMB collections: 1117-0003, 1117-0004, 1117-0006, 1117-0008, 1117-0009, 1117-0010, 1117-0012, 1117-0014, 1117-0021, 1117-0023, 1117-0029, and 1117-0056. 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.

Signing Authority

This document of the Drug Enforcement Administration was signed on December 19, 2024, by Administrator Anne Milgram. That document with the original signature and date is maintained by DEA. For administrative purposes only, and in compliance with requirements of the Office of the Federal Register, the undersigned DEA Federal Register Liaison Officer has been authorized to sign and submit the document in electronic format for publication, as an official document of DEA. This administrative process in no way alters the legal effect of this document upon publication in the Federal Register.

Heather Achbach,

[30] 44 U.S.C. 3501–3521.

Federal Register Liaison Officer,
Drug Enforcement Administration.

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)(104) through (109) as paragraphs (b)(111) through (116);

b. Redesignate paragraphs (b)(87) through (103) as paragraphs (b)(93) through (109);

c. Redesignate paragraphs (b)(84) through (86) as paragraphs (b)(89) through (91);

d. Redesignate paragraphs (b)(82) and (83) as paragraphs (b)(86) and (87);

e. Redesignate paragraphs (b)(76) through (81) as paragraphs (b)(79) through (84);

f. Redesignate paragraphs (b)(59) through (75) as paragraphs (b)(61) through (77);

g. Redesignate paragraphs (b)(21) through (58) as paragraphs (b)(22) through (59); and

h. Add new paragraphs (b)(21), (60), (78), (85), (88), (92), and (110).

The additions read as follows:

§ 1308.11 Schedule I.

* * * * *

(b) * * *

* * * * * * *	
(21) *beta*-methylacetyl fentanyl (*N*-phenyl-N-(1-(2-phenylpropyl)piperidin-4-yl)acetamide)	9868
* * * * * * *	

(60) *meta*-fluorofuranyl fentanyl (*N*-(3-fluorophenyl)-*N*-(1-phenethylpiperidin-4-yl)furan-2-carboxamide)	9871
* * * * * * *	
(78) *ortho*-chlorofentanyl (*N*-(2-chlorophenyl)-*N*-(1-phenethylpiperidin-4-yl)propionamide	9828
* * * * * * *	
(85) *ortho*-methylcyclopropyl fentanyl (*N*-(2-methylphenyl)-*N*-(1-phenethylpiperidin-4-yl)cyclopropanecarboxamide)	9849
* * * * * * *	
(88) *para*-chlorofentanyl (*N*-(4-chlorophenyl)-*N*-(1-phenethylpiperidin-4-yl)propionamide)	9818
* * * * * * *	
(92) *para*-fluoro valeryl fentanyl (*N*-(4-fluorophenyl)-*N*-(1-phenethylpiperidin-4-yl)pentanamide)	9870
* * * * * * *	
(110) tetrahydrothiofuranyl fentanyl (also known as: tetrahydrothiophene fentanyl) (*N*-(1-phenethylpiperidin-4-yl)-*N*-phenyltetrahydrothiophene-2-carboxamide)	9869
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[FR Doc. 2024-30798 Filed: 12/27/2024 8:45 am; Publication Date: 12/30/2024]