



## DEPARTMENT OF JUSTICE

### Drug Enforcement Administration

#### 21 CFR Part 1308

[Docket No. DEA-476]

### Schedules of Controlled Substances: Placement of 10 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 *N*-(1-(2-fluorophenethyl)piperidin-4-yl)-*N*-(2-fluorophenyl)propionamide (2'-fluoro *ortho*-fluorofentanyl), *N*-(1-(4-methylphenethyl)piperidin-4-yl)-*N*-phenylacetamide (4'-methyl acetyl fentanyl), *N*-(1-phenethylpiperidin-4-yl)-*N*,3-diphenylpropanamide ( $\beta$ '-phenyl fentanyl; 3-phenylpropanoyl fentanyl), *N*-phenyl-*N*-(1-(2-phenylpropyl)piperidin-4-yl)propionamide ( $\beta$ -methyl fentanyl), *N*-(2-fluorophenyl)-*N*-(1-phenethylpiperidin-4-yl)butyramide (*ortho*-fluorobutyryl fentanyl; 2-fluorobutyryl fentanyl), *N*-(2-methylphenyl)-*N*-(1-phenethylpiperidin-4-yl)acetamide (*ortho*-methyl acetylfentanyl; 2-methyl acetylfentanyl), 2-methoxy-*N*-(2-methylphenyl)-*N*-(1-phenethylpiperidin-4-yl)acetamide (*ortho*-methyl methoxyacetylfentanyl), *N*-(4-methylphenyl)-*N*-(1-phenethylpiperidin-4-yl)propionamide (*para*-methylfentanyl; 4-methylfentanyl), *N*-(1-phenethylpiperidin-4-yl)-*N*-phenylbenzamide (phenyl fentanyl; benzoyl fentanyl), *N*-(1-phenethylpiperidin-4-yl)-*N*-phenylthiophene-2-carboxamide (thiofuranyl fentanyl), including their isomers, esters, ethers, salts, and salts of isomers, esters, and ethers, in schedule I of the Controlled Substances Act. These ten specific 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 the 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. 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, reverse distribute, import, export, engage in research, conduct instructional activities or chemical analysis, or possess), or propose to handle 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ '-phenyl fentanyl,  $\beta$ -methyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl.

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

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 DATE OF PUBLICATION IN THE FEDERAL REGISTER].

**ADDRESSES:** To ensure proper handling of comments, please reference "Docket No. DEA-476" on all electronic and written correspondence, including any attachments.

- *Electronic comments:* Interested persons may file written comments on this proposal in accordance with 21 CFR 1308.43(g). The Drug Enforcement Administration (DEA) 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. 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 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/DPW, 8701 Morrisette Drive, Springfield, Virginia 22152.

- *Hearing requests:* 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. All requests for hearing and waivers of participation must be sent to: Drug Enforcement Administration, Attn: Administrator, 8701 Morrisette Drive, Springfield, Virginia 22152. All requests for hearing and waivers of participation should also be sent to: (1) Drug Enforcement Administration, Attn: Hearing Clerk/OALJ, 8701 Morrisette Drive, Springfield, Virginia 22152; and (2) Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrisette Drive, Springfield, Virginia 22152.

**FOR FURTHER INFORMATION CONTACT:** Terrence L. Boos, Drug and Chemical Evaluation Section, Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrisette Drive, Springfield, Virginia 22152; Telephone: (571) 362–3249

**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 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, 5 U.S.C. 551–559. 21 CFR 1308.41–1308.45; 21 CFR part 1316, subpart D. Interested persons may file requests for hearing or notices of intent to participate in a hearing in conformity with the requirements of 21 CFR 1308.44(a) or (b), and include a statement of interest in the proceeding and the objections or issues, if any, concerning which the person desires to be heard. Any interested person may file a waiver of an opportunity for a hearing or to participate in a hearing together with a written statement regarding the interested person’s position on the matters of fact and law involved in any hearing as set forth in 21 CFR 1308.44(c).

All requests for a hearing and waivers of participation must be sent to DEA using the address information provided above.

### **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 (delegated to the Administrator of DEA pursuant to 28 CFR 0.100) on his own motion. 21 U.S.C. 811(a). This proposed action is supported by a recommendation from the Assistant Secretary for Health of U.S. Department of Health and Human Services (HHS) (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 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ '-phenyl fentanyl,  $\beta$ -methyl fentanyl, *ortho*-

fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl.

## **Background**

On February 6, 2018, pursuant to 21 U.S.C. 811(h)(1), the then-Acting Administrator of 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 upon finding that these substances pose an imminent hazard to the public safety. The 10 substances named in this proposed rule (2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl) meet the existing definition of fentanyl-related substances. On April 19, 2019, DEA specifically identified four of these 10 substances (2'-fluoro *ortho*-fluorofentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-methyl acetylfentanyl, and thiofuranyl fentanyl) as meeting the definition of fentanyl-related substances. 84 FR 16397. Although DEA did not issue a *Federal Register* publication to identify the other six substances, the February 6, 2018, temporary scheduling order emphasized that, even still, a substance is controlled by virtue of the order if it falls within the definition of fentanyl-related substances. 83 FR 5188, 5189. As discussed below in Factor 3, all 10 substances meet the definition as they are not otherwise controlled in any other schedule (i.e., not included under another Administration 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 10 specific substances already covered by that order, was set to expire on February 6, 2020. However, as explained in DEA's

April 10, 2020, correcting amendment (85 FR 20155), Congress overrode and extended that expiration date until May 6, 2021, by enacting on February 6, 2020 the Temporary Reauthorization and Study of the Emergency Scheduling of Fentanyl Analogues Act (Pub. L. 116-114, sec. 2, 134 Stat. 103). By operation of law, the temporary control of fentanyl-related substances, which includes these 10 covered substances, will remain in effect until May 6, 2021, unless DEA permanently places them in schedule I prior to May 6, 2021. As discussed in the above Legal Authority section, proceedings under 21 U.S.C. 811(a) may be initiated by the Administrator of DEA on his own motion.

The Acting Administrator, on his own motion, is initiating proceedings to permanently schedule the following 10 fentanyl-related substances: 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ '-phenyl fentanyl,  $\beta$ -methyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl. DEA gathered the available information regarding the pharmacology, chemistry, trafficking, actual abuse, pattern of abuse, and the relative potential for abuse for these 10 fentanyl-related substances, as well as for six other fentanyl-related substances (benzodioxole fentanyl, crotonyl fentanyl, fentanyl carbamate, *ortho*-fluoro isobutyryl fentanyl, *ortho*-fluoroacryl fentanyl, and *para*-fluoro furanyl fentanyl). On April 3, and October 2, 2019, the then-Acting Administrator submitted this data to the Assistant Secretary, and requested that HHS provide DEA with a scientific and medical evaluation and a scheduling recommendation for the 16 fentanyl-related substances named above, in accordance with 21 U.S.C. 811(b) and (c).

Upon evaluating the scientific and medical evidence, on July 2, 2020, the Assistant Secretary submitted to the Acting Administrator, HHS's scientific and medical evaluation and scheduling recommendation for 11 of the 16 fentanyl-related substances,

including the 10 named substances in this proposed rule as well as crotonyl fentanyl.<sup>1</sup> Upon receipt of the scientific and medical evaluation and scheduling recommendation from HHS, DEA reviewed these documents and all other relevant data, and conducted its own eight-factor analysis of the abuse potential of the 10 substances in accordance with 21 U.S.C. 811(c). On October 2, 2020, DEA issued a final order (85 FR 62215) for crotonyl fentanyl to remain as a schedule I substance under the CSA in order to meet the United States' obligations under the 1961 Single Convention on Narcotic Drugs (Single Convention), March 30, 1961, 18 U.S.T. 1407, 570 U.N.T.S. 151, as amended.<sup>2</sup> As such, crotonyl fentanyl will not be discussed further in this scheduling action.

**Proposed Determination to Permanently Schedule 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl**

As discussed in the background section, the Acting Administrator is initiating proceedings to permanently add 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl to schedule I. DEA has reviewed the scientific and medical evaluation and scheduling recommendation from HHS, and all other relevant data, and conducted its own eight-factor analysis of the abuse potential of these 10 substances. 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. Please note that both

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<sup>1</sup> HHS' scientific and medical evaluation for the other five fentanyl-related substances (benzodioxole fentanyl, fentanyl carbamate, *ortho*-fluoro isobutyryl fentanyl, *ortho*-fluoroacryl fentanyl, and *para*-fluoro furanyl fentanyl) is ongoing. DEA will not further discuss these five substances in this proposed rule.

<sup>2</sup> In November 2019, the Director-General of the World Health Organization recommended to the Secretary-General that crotonyl fentanyl be placed in Schedule I of the Single Convention. On May 7, 2020, the Secretary-General advised the Secretary of State of the United States, by letter, that during its 63rd session in March 2020, the Commission on Narcotic Drugs voted to place crotonyl fentanyl in Schedule I of the Single Convention (CND Mar/63/2).

the DEA and HHS 8-Factor analyses and the Assistant Secretary's July 2, 2020, 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-476."

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 that DEA consider the following criteria when determining whether a particular drug or substance has a potential for abuse:<sup>3</sup>

- 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 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl is associated with their pharmacological similarity to other schedule I and II mu-opioid receptor agonist substances, which have a high

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<sup>3</sup> 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.

potential for abuse. Similar to morphine and fentanyl, these 10 substances have been shown to bind and act as mu-opioid receptor agonists.

These 10 substances have no approved medical use in the United States and have been encountered on the illicit drug market. The use of some fentanyl-related substances has been associated with adverse health outcomes, including death. The appearance of several substances structurally related to fentanyl in the illicit drug market has resulted in a significant increase in drug overdose deaths in the United States. According to the Centers for Disease Control and Prevention (CDC) overdose death data for 2018, there continues to be an increase in the number of deaths related to synthetic opioids. Opioids were involved in about 70 percent of all drug-involved overdose deaths in 2018. Further, CDC reports demonstrate that the increase in synthetic opioid overdose deaths are largely attributed to an increase in the supply of illicitly manufactured fentanyl and substances structurally related to fentanyl. Because 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl 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 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl is without medical advice, and accordingly leads to the conclusion that these 10 substances are abused for their opioidergic properties.

There are no legitimate drug channels for 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-

methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl as marketed FDA-approved drug products, but these substances are available for purchase from legitimate chemical companies for research purposes. However, despite the limited legitimate research use of these 10 substances, reports from public health and law enforcement data indicate that all 10 substances 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 abuse<sup>4</sup> within the United States. According to the National Forensic Laboratory Information System (NFLIS),<sup>5</sup> which collects and analyzes drug exhibits submitted to Federal, State, and local forensic laboratories, there were 235 total reports of seven of the 10 substances (4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl) between 2017 and 2020 (queried on July 16, 2020). In 2017 and 2018, U.S. Customs and Border Protection (CBP) reported that two other of the 10 substances (2'-fluoro *ortho*-fluorofentanyl and  $\beta'$ -phenyl fentanyl) have been positively identified in seized drugs, respectively. In 2018, *ortho*-methyl methoxyacetyl fentanyl was positively identified in an exhibit submitted to NMS laboratories for analysis by the Department of Homeland Security. Consequently, the positive identification of the 10 substances in law enforcement encounters indicates that these substances are being abused, and thus pose safety hazards to the health of users.

2. *Scientific Evidence of the Drug's Pharmacological Effects, if Known: 2'-fluoro ortho-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, ortho-fluorobutyryl fentanyl, ortho-methyl acetylfentanyl, ortho-methyl methoxyacetyl fentanyl, para-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl*

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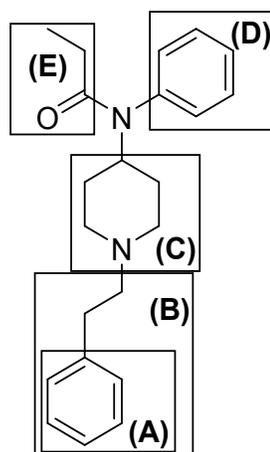
<sup>4</sup> While law enforcement data is not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. See 76 FR 77330, 77332, Dec. 12, 2011.

<sup>5</sup> 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.

are pharmacologically similar to other schedule I and schedule II mu-opioid receptor agonist substances. The abuse potential (assessed by drug discriminative studies) of 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl show that these substances share discriminative stimulus effects similar to fentanyl and morphine. Similar to schedule I and II opioid analgesics, these 10 substances bind to and activate the mu-opioid receptor. Additionally, behavioral studies in animals demonstrate these 10 substances produce analgesic effects similar to fentanyl and morphine. Pre-treatment with naltrexone, an opioid antagonist, attenuated analgesic effect of these 10 substances, as well as fentanyl and morphine. These data indicate that the 10 substances are mu-opioid receptor agonists with effects on the central nervous system. Data from drug discrimination studies showed that these 10 substances share discriminative stimulus effects similar to those of morphine. Thus, it is concluded from *in vitro* and *in vivo* pharmacological studies that the effects of the 10 substances are similar to that of fentanyl and morphine and are mediated by mu-opioid receptor agonism.

3. *The State of Current Scientific Knowledge Regarding the Drug or Other Substance: 2'-Fluoro ortho-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, ortho-fluorobutyryl fentanyl, ortho-methyl acetylfentanyl, ortho-methyl methoxyacetyl fentanyl, para-methylylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl are synthetic opioids of the 4-anilidopiperidine structural class, which includes fentanyl. As defined in the February 6, 2018, temporary 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, alkoxy, hydroxyl, halo, haloalkyl, amino or nitro groups;
- (C) substitution in or on the piperidine ring with alkyl, alkenyl, alkoxy, 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 any one, or any combination, of above-mentioned modifications (see Figure 1) would meet the structural requirements of the definition of fentanyl-related substances. The present 10 substances fall within the definition of fentanyl-related substances by the following modifications:

1. 2'-fluoro *ortho*-fluorofentanyl: substitution on the phenethyl group with a halo group and substitution on the aniline ring (meets definition for modifications B and D);

2. 4'-methyl acetyl fentanyl: substitution on the phenethyl group with an alkyl group and replacement of the *N*-propionyl group by another acyl group (meets definition for modifications B and E);
3.  $\beta$ -methyl fentanyl: substitution on the phenethyl group with an alkyl group (meets definition for modification B);
4.  $\beta'$ -phenyl fentanyl: replacement of the *N*-propionyl group by another acyl group (meets definition for modification E);
5. *ortho*-fluorobutyryl fentanyl: substitution on the aniline ring and replacement of the *N*-propionyl group with another acyl group (meets definition for modifications D and E);
6. *ortho*-methyl acetylfentanyl: substitution on the aniline ring and replacement of the *N*-propionyl group with another acyl group (meets definition for modifications D and E);
7. *ortho*-methyl methoxyacetylfentanyl: substitution on the aniline ring and replacement of the *N*-propionyl group with another acyl group (meets definition for modifications D and E);
8. *para*-methylfentanyl: substitution on the aniline ring (meets definition for modification D);
9. phenyl fentanyl: replacement of the *N*-propionyl group by another acyl group (meets definition for modification E); and
10. thiofuranyl fentanyl: replacement of the *N*-propionyl group by another acyl group (meets definition for modification E).

No study has been undertaken to evaluate the efficacy, toxicology, and safety of the 10 substances in humans. It can be inferred from data obtained from animal studies that these 10 substances have sufficient distribution to the brain to produce depressant effects similar to that of other mu-opioid receptor agonists such as fentanyl. Data from *in*

*vitro* receptor binding studies show that these 10 substances, similar to fentanyl, display high selectivity for the mu-opioid receptor over other opioid receptor subtypes.

There are no FDA-approved marketing applications for a drug product containing 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl for any therapeutic indication in the United States. Moreover, there are no clinical studies or petitions which have claimed an accepted medical use in the United States for these 10 substances.

4. *Its History and Current Pattern of Abuse: 2'-Fluoro ortho-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, ortho-fluorobutyryl fentanyl, ortho-methyl acetylfentanyl, ortho-methyl methoxyacetyl fentanyl, para-methylylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl, like other substances structurally related to fentanyl, are disguised as a “legal” alternative to fentanyl. Between 2017 and 2020, law enforcement officials in the United States encountered these 10 substances.*

5. *The Scope, Duration, and Significance of Abuse: 2'-Fluoro ortho-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, ortho-fluorobutyryl fentanyl, ortho-methyl acetylfentanyl, ortho-methyl methoxyacetyl fentanyl, para-methylylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl, similar to other substances structurally related to fentanyl, are often used as recreational drugs. The recreational use of these 10 substances and other fentanyl-related substances continues to be of significant concern as the United States currently is in the midst of an opioid epidemic. These substances are distributed to users, often with unpredictable outcomes. Because users of these fentanyl-related substances and their associated drug products 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 abusers. Evidence that these 10 substances are being abused and trafficked is confirmed by law enforcement encounters. NFLIS contained 235 reports of 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *para*-methylylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl from Federal, State, and local forensic laboratories between 2017 and 2020. In 2017 and 2018, CBP reported that 2'-fluoro *ortho*-fluorofentanyl and  $\beta'$ -phenyl fentanyl have been positively identified in seized drugs, respectively. In 2018, *ortho*-methyl methoxyacetyl fentanyl was positively identified in an exhibit submitted to NMS laboratories for analysis by the Department of Homeland Security.

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 structurally related substances in the illicit drug market. These substances have a history of being trafficked as replacements for heroin and other synthetic opioids. Increasingly, law enforcement has encountered fentanyl and substances structurally related to fentanyl in counterfeit prescription opioids, heroin, and other street drugs such as cocaine, methamphetamine, and synthetic cannabinoids. 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, as defined in the February 6, 2018, temporary order, have similar chemical structure to fentanyl, these substances are expected to have similar biological effects. In *in vitro* and *in vivo* studies, 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl produced pharmacological effects similar to

fentanyl. Thus, these 10 substances pose the same qualitative public health risks as heroin, fentanyl, and other mu-opioid receptor agonists.

According to a CDC report, from 2013 to 2017, opioid-related overdose deaths in the United States increased 90 percent from 25,052 to 47,600. The increase in the number of opioid-related deaths was primarily driven by illicitly manufactured fentanyl<sup>6</sup>. According to CDC 2018 provisional data, there were 68,500 drug overdose fatalities; of those, 47,600 (~ 69 percent) involved an opioid. The use of some fentanyl-related substances has been associated with adverse health outcomes, including death.

7. *Its Psychic or Physiological Dependence Liability:* There are no pre-clinical and clinical studies that have evaluated the dependence potential of 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl. These 10 substances are mu-opioid receptor agonists, and discontinuation of the use of mu-opioid receptor agonists such as fentanyl and morphine is known to cause withdrawal indicative of physical dependence. Opioid withdrawal includes nausea and vomiting, depression, agitation, anxiety, craving, sweats, hypertension, diarrhea, and fever.

8. *Whether the Substance Is an Immediate Precursor of a Substance Already Controlled Under the CSA:* 2'-Fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl are not considered immediate precursors of any controlled substance of the CSA as defined by 21 U.S.C. 802(23).

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<sup>6</sup> If evidence of prescription or illicit use was not available, fentanyl was categorized as illicitly-manufactured fentanyl ("IMF") because the vast majority of fentanyl overdose deaths involve IMF. Gladden RM, O'Donnell J, Mattson CL, Seth P. Changes in Opioid-Involved Overdose Deaths by Opioid Type and Presence of Benzodiazepines, Cocaine, and Methamphetamine - 25 States, July-December 2017 to January-June 2018. MMWR Morb Mortal Wkly Rep. 30; 68(34):737-744.

*Conclusion:* After considering the scientific and medical evaluation conducted by HHS, HHS's scheduling recommendation, and DEA's own eight-factor analysis, DEA finds that the facts and all relevant data constitute substantial evidence of the potential for abuse of 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl. As such, DEA hereby proposes to permanently schedule 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl in schedule I of 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 Health of HHS and review of all other available data, the Acting Administrator of DEA, pursuant to 21 U.S.C. 811(a) and 21 U.S.C. 812(b)(1), finds that:

**1) 2'-Fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl have a high potential for abuse.**

According to HHS, 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylylfentanyl, phenyl

fentanyl, and thiofuranyl fentanyl, similar to fentanyl, are mu-opioid receptor agonists. These substances have analgesic effects, and these effects are mediated by mu-opioid receptor agonism. HHS states that substances that produce mu-opioid receptor agonist effects in the central nervous system (*e.g.*, morphine and fentanyl) are considered as having a high potential for abuse. Data obtained from drug discrimination studies indicate that 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl fully substituted for the discriminative stimulus effects of morphine.

**2) 2'-Fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl have no currently accepted medical use in treatment in the United States.**

According to HHS, there are no FDA-approved new drug applications for 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl in the United States. There are no known therapeutical applications for these fentanyl-related substances and thus they have no currently accepted medical use in the United States.<sup>7</sup>

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<sup>7</sup> Although there is no evidence suggesting that 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylylfentanyl, phenyl fentanyl, and thiofuranyl 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:

**3) There is a lack of accepted safety for use of 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl under medical supervision.**

Because 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl have no FDA-approved medical use and have not been thoroughly investigated as new drugs, their safety for use under medical supervision is undetermined. Thus, there is a lack of accepted safety for use of 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl under medical supervision.

Based on these findings, the Acting Administrator of DEA concludes that 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl, including their isomers, esters, ethers, salts, and salts of isomers, esters, and ethers warrant continued control in schedule I of the CSA. 21 U.S.C. 812(b)(1).

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- 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.

**Requirements for Handling 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl.**

If this rule is finalized as proposed, 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl would continue<sup>8</sup> to be subject to the CSA's schedule I regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, reverse distribution, dispensing, importation, exportation, research, and conduct of instructional activities, including the following:

1. *Registration.* Any person who handles (manufactures, distributes, reverse distributes, dispenses, imports, exports, engages in research, or conducts instructional activities or chemical analysis with, or possesses) 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl, or who desires to handle 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl is required to 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.

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<sup>8</sup> 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl, are covered by the February 6, 2018, temporary scheduling order, and are currently subject to schedule I controls on a temporary basis, pursuant to 21 U.S.C. 811(h). 83 FR 5188.

2. *Security.* 2'-Fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl 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. Non-practitioners handling 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl also must comply with the employee screening requirements of 21 CFR 1301.90 -1301.93.

3. *Labeling and Packaging.* All labels and labeling for commercial containers of 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl 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 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl 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 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl 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 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl 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 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl 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 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl 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 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl 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 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl 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 (Regulatory Planning and Review) and 13563 (Improving Regulation and 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.

*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 Acting Administrator, in accordance with the Regulatory Flexibility Act, 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 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). DEA estimates that all entities handling or planning to handle 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl have already established and implemented the systems and processes required to handle these substances which meet the definition of fentanyl-related substances.

There are currently 57 registrations authorized to handle the fentanyl-related substances as a class, which include 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl, as well as a number of registered analytical labs that are authorized to handle schedule I controlled substances generally. These 57

registrations represent 51 entities, of which eight are small entities. Therefore, DEA estimates eight small entities are affected by this proposed rule.

A review of the 57 registrations indicates that all entities that currently handle fentanyl-related substances, including 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl, also handle other schedule I controlled substances, and have established and implemented (or maintain) the systems and processes required to handle 2'-fluoro *ortho*-fluorofentanyl, 4'-methyl acetyl fentanyl,  $\beta$ -methyl fentanyl,  $\beta'$ -phenyl fentanyl, *ortho*-fluorobutyryl fentanyl, *ortho*-methyl acetylfentanyl, *ortho*-methyl methoxyacetyl fentanyl, *para*-methylfentanyl, phenyl fentanyl, and thiofuranyl fentanyl. 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 eight affected small entities. Therefore, DEA has concluded that this proposed rule will not have a significant effect 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 million 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 paragraph (75) as paragraph (b)(84);
- b. Add paragraph (b)(83);
- c. Redesignate paragraphs (b)(65) through (71) as paragraphs (b)(76) through (82);
- d. Add a new paragraph (b)(75);
- e. Redesignate paragraphs (b)(60) through (64) as paragraphs (b)(70) through (74);
- f. Add a new paragraph (69);
- g. Redesignate paragraphs (b)(56) through (59) as paragraphs (b)(65) through (68);
- h. Add a new paragraph (64);
- i. Redesignate paragraph (b)(55) as paragraph (b)(63);
- j. Add new paragraphs (b)(61) and (62);

- k. Redesignate paragraphs (b)(45) through (54) as paragraphs (b)(51) through (60);
- l. Add new paragraph (b)(50);
- m. Redesignate paragraphs (b)(37) through (44) as paragraphs (b)(42) through (49);
- n. Add a new paragraph (b)(41);
- o. Redesignate paragraph (b)(36) as paragraph (b)(40);
- p. Add a reserved paragraph (b)(39);
- q. Redesignate paragraphs (b)(22) through (35) as paragraphs (b)(25) through (38);
- r. Add a reserved paragraph (b)(24);
- s. Redesignate paragraphs (b)(17) through (21) as paragraphs (b)(19) through (23); and
- t. Add new paragraphs (b)(17) and (18).

The additions to read as follows:

**§ 1308.11 Schedule I.**

\* \* \* \* \*

(b) \* \* \*

(17) Beta-methyl fentanyl (*N*-phenyl-*N*-(1-(2-phenylpropyl)piperidin-4-yl)propionamide; other name: β-methyl fentanyl).....9856

(18) Beta'-phenyl fentanyl (*N*-(1-phenethylpiperidin-4-yl)-*N*,3-diphenylpropanamide; other names: β'-phenyl fentanyl; 3-phenylpropanoyl fentanyl).....9842

\* \* \* \* \*

(41) 2'-Fluoro *ortho*-fluorofentanyl (*N*-(1-(2-fluorophenethyl)piperidin-4-yl)-*N*-(2-fluorophenyl)propionamide; other name: 2'-fluoro 2-fluorofentanyl).....9829

\* \* \* \* \*

(50) 4'-Methyl acetyl fentanyl (*N*-(1-(4-methylphenethyl)piperidin-4-yl)-*N*-phenylacetamide).....9819

\* \* \* \* \*

(61) *ortho*-Fluorobutyryl fentanyl (*N*-(2-fluorophenyl)-*N*-(1-phenethylpiperidin-4-yl)butyramide; other name: 2-fluorobutyryl fentanyl).....9846

(62) *ortho*-Methyl acetylfentanyl (*N*-(2-methylphenyl)-*N*-(1-phenethylpiperidin-4-yl)acetamide; other name: 2-methyl acetylfentanyl) .....9848

\* \* \* \* \*

(64) *ortho*-Methyl methoxyacetyl fentanyl (2-methoxy-*N*-(2-methylphenyl)-*N*-(1-phenethylpiperidin-4-yl)acetamide; other name: 2-methyl methoxyacetyl fentanyl).....9820

\* \* \* \* \*

(69) *para*-Methylfentanyl (*N*-(4-methylphenyl)-*N*-(1-phenethylpiperidin-4-yl)propionamide; other name: 4-methylfentanyl).....9817

\* \* \* \* \*

(75) Phenyl fentanyl (*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylbenzamide; other name: benzoyl fentanyl).....9841

\* \* \* \* \*

(83) Thiofuranyl fentanyl (*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylthiophene-2-carboxamide; other names: 2-thiofuranyl fentanyl; thiophene fentanyl).....9839

\* \* \* \* \*

**D. Christopher Evans,**

Acting Administrator.

[FR Doc. 2021-04214 Filed: 3/2/2021 8:45 am; Publication Date: 3/3/2021]