



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2017-N-4515]

International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; Oxycodone, Carfentanyl, Pregabalin, Tramadol, Cannabidiol, Ketamine, and Eleven Other Substances; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is requesting interested persons to submit comments concerning abuse potential, actual abuse, medical usefulness, trafficking, and impact of scheduling changes on availability for medical use of 17 drug substances. These comments will be considered in preparing a response from the United States to the World Health Organization (WHO) regarding the abuse liability and diversion of these drugs. WHO will use this information to consider whether to recommend that certain international restrictions be placed on these drugs. This notice requesting comments is required by the Controlled Substances Act (the CSA).

DATES: Submit either electronic or written comments by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before

[INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The <https://www.regulations.gov> electronic filing system will accept comments

until midnight Eastern Time at the end of [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

### *Electronic Submissions*

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

### *Written/Paper Submissions*

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in “Instructions.”

*Instructions:* All submissions received must include the Docket No. FDA-2017-N-4515 for “International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; Ocfentanil; Furanyl fentanyl (Fu-F); Acryloylfentanyl (Acrylfentanyl); Carfentanil; 4-fluoroisobutyrfentanyl (4-FIBF); Tetrahydrofuranylfentanyl (THF-F); 4-fluoroamphetamine (4-FA); AB-PINACA; AB-CHMINACA; 5F-PB-22; UR-144; 5F-ADB; Etizolam; Pregabalin; Tramadol; Cannabidiol; Ketamine; Request for Comments.” Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed

confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

*Docket:* For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: James R. Hunter, Center for Drug Evaluation and Research, Controlled Substance Staff, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 5150, Silver Spring, MD 20993-0002, 301-796-3156, email: [james.hunter@fda.hhs.gov](mailto:james.hunter@fda.hhs.gov).

#### SUPPLEMENTARY INFORMATION:

##### I. Background

The United States is a party to the 1971 Convention on Psychotropic Substances (Psychotropic Convention). Article 2 of the Psychotropic Convention provides that if a party to

the convention or WHO has information about a substance, which in its opinion may require international control or change in such control, it shall so notify the Secretary-General of the United Nations (the U.N. Secretary-General) and provide the U.N. Secretary-General with information in support of its opinion.

Section 201 of the CSA (21 U.S.C. 811) (Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970) provides that when WHO notifies the United States under Article 2 of the Psychotropic Convention that it has information that may justify adding a drug or other substances to one of the schedules of the Psychotropic Convention, transferring a drug or substance from one schedule to another, or deleting it from the schedules, the Secretary of State must transmit the notice to the Secretary of Health and Human Services (Secretary of HHS). The Secretary of HHS must then publish the notice in the *Federal Register* and provide opportunity for interested persons to submit comments that will be considered by HHS in its preparation of the scientific and medical evaluations of the drug or substance.

## II. WHO Notification

The Secretary of HHS received the following notice from WHO (non-relevant text removed):

Ref.: C.L.xx.2017

The World Health Organization (WHO) presents its compliments to Member States and Associate Members and has the pleasure of informing that the Thirty-ninth Expert Committee on Drug Dependence (ECDD) will meet in Geneva from 6 to 10 November 2017 to review a number of substances with potential for dependence, abuse and harm to health, and will make recommendations to the U.N. Secretary-General, on the need for and level of international control of these substances.

At its 126th session in January 2010, the Executive Board approved the publication "Guidance on the WHO review of psychoactive substances for international control" (EB126/2010/REC1, Annex 6) which requires the Secretariat to request relevant information from Ministers of Health in Member States to prepare a report for submission to the ECDD. For this purpose, a questionnaire was designed to gather information on the legitimate use, harmful use, status of national control and potential impact of international control for each substance under evaluation. Member States are

invited to collaborate, as in the past, in this process by providing pertinent information as requested in the questionnaire and concerning substances under review.

It would be appreciated if a person from the Ministry of Health could be designated as the focal point responsible for coordinating and answering the questionnaire. (non relevant information from letter not shown, see letter for text not shown here) The designated focal point, and only this person, should access and complete the questionnaires:

1. Ocfentanil
2. Furanyl fentanyl (Fu-F)
3. Acryloylfentanyl (Acrylfentanyl)
4. Carfentanil
5. 4-fluoroisobutyrfentanyl (4-FIBF)
6. Tetrahydrofuranylfentanyl (THF-F)
7. 4-fluoroamphetamine (4-FA)
8. AB-PINACA
9. AB-CHMINACA
10. 5F-PB-22
11. UR-144
12. 5F-ADB
13. Etizolam
14. Pregabalin
15. Tramadol
16. Cannabidiol
17. Ketamine

PDF versions of the questionnaire in English, French and Spanish may be downloaded from the link <http://www.who.int/medicines/access/controlled-substances/ecdd/en/>. Please note that these versions are for reference only and all questionnaires must be answered through the online system. Further clarification regarding the questionnaire may be obtained from the Secretariat by emailing: [ecddsecretariat@who.int](mailto:ecddsecretariat@who.int).

Replies to the questionnaire must reach the Secretariat by 30 September 2017 in order to facilitate analyses and preparation of the report before the planned meeting. Where there is a competent National Authority under the International Drug Control Treaties, it is kindly requested that the questionnaire be completed in collaboration with such body.

The summary information from the questionnaire will be published online as part of the report on the website for the Thirty-ninth ECDD linked to the Department of Essential Medicines and Health Products (EMP). The provisional agenda of the Thirty-ninth ECDD and the list of psychoactive substances under review are also published on Thirty-ninth ECDD web page: <http://www.who.int/medicines/access/controlled-substances/ecdd/en/>.

Member States are also encouraged to provide any additional relevant information (unpublished or published) that is available on these substances to: [ecddsecretariat@who.int](mailto:ecddsecretariat@who.int). This information will be an invaluable contribution to the ECDD and all submissions will be treated as confidential.

The World Health Organization takes this opportunity to renew to Member States and Associate Members the assurance of its highest consideration.

GENEVA, 7 July 2017

FDA has verified the website addresses contained in the WHO notice, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

### III. Substances Under WHO Review

Ocfentanil is a synthetically produced opioid that is structurally related to fentanyl and approximately equipotent in effect. Reported risks associated with use of ocfentanil include development of opioid use disorder, overdose, and fatal overdose. It has no approved medical use in the United States and is not a controlled substance in the United States under the CSA.

Furanyl fentanyl (Fu-F) is a potent clandestinely produced synthetic opioid that is an analog of fentanyl. Evidence suggests that the pattern of abuse of fentanyl analogues, including furanyl fentanyl, parallels that of heroin and prescription opioid analgesics. Fu-F produces the typical opioid effects that include respiratory depression and loss of consciousness. Seizures of Fu-F have been encountered in powder form. Fu-F has been connected to fatal overdoses, in

which intravenous routes of administration are documented. It has no approved medical use in the United States. On November 29, 2016, the Drug Enforcement Administration (DEA) issued a final order to temporarily schedule Fu-F and its isomers, esters, ethers, salts and salts of isomers, esters and ethers, into Schedule I pursuant to the temporary scheduling provisions of the CSA.

Acryloylfentanyl (Acrylfentanyl) belongs to the 4-anilidopiperidine class of synthetic opioids and is similar in structure to fentanyl. Acryloylfentanyl is a clandestinely produced analog of fentanyl and sold illegally as a research chemical on several websites.

Acryloylfentanyl has also been associated with adverse events typically associated with opioid use such as respiratory depression, anxiety, constipation, tiredness, hallucinations, and withdrawal. The use of acryloylfentanyl has also been linked to the development of opioid use disorder, overdose, and fatal overdose. Acryloylfentanyl has no commercial or medical uses. On July 14, 2017, the DEA issued a temporary order to temporarily schedule acryloylfentanyl, its isomers, esters, ethers, salts and salts of isomers, esters, and ethers, into Schedule I pursuant to the temporary scheduling provisions of the CSA.

Carfentanil, also known as 4-carbomethoxyfentanyl, is an extremely potent synthetic opioid that is similar in structure to and approximately 100 times more potent than fentanyl as an analgesic. At one time legitimately produced, carfentanil is no longer manufactured, marketed, or used in the United States; it is approved by FDA for use under restricted conditions by veterinarians as a immobilizing agent for certain large animals. Illicitly produced carfentanil is a particularly harmful fentanyl analogue that is also being laced into heroin or sold by itself and trafficked in the United States. It is not approved for human use. Drug seizure data indicate that carfentanil is typically used in small doses to cut heroin and other illicitly abused drugs. The



significant risk to public health associated with carfentanil use stems from its respiratory depressive effects with very small amounts. Several fatalities have been reported as the result of carfentanil overdoses. On October 28, 1988, the DEA placed carfentanil in Schedule II of the CSA.

4-fluoroisobutyrfentanyl is a clandestinely produced synthetic opioid that is an analog of fentanyl. It has  $\mu$ -receptor agonist activity similar to that of fentanyl. This would result in effects associated with opioid agonists such as analgesia, respiratory depression, anxiety, constipation, tiredness, hallucinations, withdrawal, the development of opioid use disorder, overdose, and fatal overdose. The use of 4-fluoroisobutyrfentanyl has been implicated in several cases of overdose and fatal overdoses. 4-fluoroisobutyrfentanyl has not been approved for medical use in the U.S. On May 3, 2017, the DEA issued a temporary order to temporarily schedule 4-fluoroisobutyrfentanyl, its isomers, esters, ethers, salts and salts of isomers, esters and ethers, into Schedule I pursuant to the temporary scheduling provisions of the CSA.

Tetrahydrofuranylfentanyl (THF-F) is a synthetic opioid that is an analog of fentanyl. It has  $\mu$ -receptor agonist activity similar to that of fentanyl, resulting in effects associated with opioid agonists such as analgesia, respiratory depression, anxiety, constipation, tiredness, hallucinations, withdrawal, the development of opioid use disorder, overdose, and fatal overdose. THF-F is not approved for medical use or controlled in the United States under the CSA.

4-Fluoroamphetamine (4-FA) is a psychoactive substance of the phenethylamine and substituted amphetamine chemical classes and produces stimulant effects. WHO reports that 4-FA is clandestinely produced, and its use is associated with fatal and non-fatal intoxications. 4-FA was reviewed at the 37th ECDD (2015) and, while not placed under international control due

to insufficient data, was kept under surveillance. 4-FA is not approved for medical use in the United States and it is not controlled under the CSA.

AB-PINACA is a clandestinely produced synthetic cannabinoid agonist approximately 1.5 times as potent as delta-9-tetrahydrocannabinol. Adverse effects produced by cannabinoid agonists include tachycardia, agitation, hallucination, chest pain, seizure, anxiety, acute psychosis, and death. AB-PINACA has been detected in illicit synthetic cannabinoid substances, and reported in cases of overdose and hospitalizations. It has not been approved for medical use in the United States. On January 27, 2017, the DEA published a Notice of Proposed Rulemaking to permanently control AB-PINACA as a Schedule I substance under the CSA.

AB-CHMINACA is a clandestinely produced synthetic cannabinoid agonist that is approximately 16 times more potent than delta-9-tetrahydrocannabinol. Adverse effects produced by cannabinoid agonists include tachycardia, agitation, hallucination, chest pain, seizure, anxiety, acute psychosis, and death. AB-CHMINACA has been detected in illicit synthetic cannabinoid substances and found in cases of overdose and hospitalizations. AB-CHMINACA has not been pre-reviewed or critically reviewed by the WHO. On January 27, 2017, the DEA published a Notice of Proposed Rulemaking to permanently control AB-CHMINACA as a Schedule I substance under the CSA.

5F-PB-22 is a synthetic cannabinoid agonist with similar effects to delta-9-tetrahydrocannabinol, one of the main psychoactive components of cannabis. Adverse effects produced by cannabinoid agonists include tachycardia, agitation, hallucination, chest pain, seizure, anxiety, acute psychosis, and death. 5F-PB-22 is clandestinely produced. It has been found laced on plant material and marketed as herbal products, and is smoked for its psychoactive effects. According to the WHO, 5F-PB-22 has been associated with fatal

intoxications. On September 6, 2016, the DEA issued a final rule to permanently place 5F-PB-22 into Schedule I of the CSA.

UR-144 is a clandestinely produced synthetic cannabinoid agonist. In general, adverse effects produced by cannabinoid agonists include tachycardia, agitation, hallucination, chest pain, seizure, anxiety, and acute psychosis. UR-144 has been detected in herbal smoking blends that are sold as herbal incense. In June 2014, the 36th (2014) ECDD reviewed UR-144 and recommended that it be placed under surveillance. On May 11, 2016, the DEA issued a final rule to permanently schedule UR-144 into Schedule I of the CSA.

5F-ADB is a clandestinely produced synthetic cannabinoid agonist. In general, adverse effects produced by cannabinoid agonists include tachycardia, agitation, hallucination, chest pain, seizure, anxiety, and acute psychosis. 5F-ADB has been identified in overdose and/or cases involving death attributed to their abuse. Adverse health effects reported from incidents involving 5F-ADB and other synthetic cannabinoids have included: Nausea, persistent vomiting, agitation, altered mental status, seizures, convulsions, loss of consciousness, and/or cardio toxicity. On April 10, 2017, the DEA issued a temporary scheduling order to temporarily schedule 5F-ADB, its isomers, esters, ethers, salts and salts of isomers, esters, and ethers into Schedule I pursuant to the temporary scheduling provisions of the CSA.

Etizolam belongs to a class of substances known as benzodiazepines. Benzodiazepines produce central nervous system depression and are commonly used to treat insomnia, anxiety, and seizure disorders. Etizolam is currently prescribed in some countries to treat generalized anxiety disorder with depressive symptoms, but is not approved for medical use or controlled in the United States under the CSA. WHO reported that non-fatal intoxications that include cases of driving under the influence of drugs have been linked to etizolam. The ECDD at its 37th

(2015 meeting reviewed etizolam and recommended that a critical review of etizolam is warranted.

Pregabalin is an anticonvulsant-type drug used to treat pain generated from the nervous system. It is available as an oral capsule and oral solution and approved for medical use in the United States for the management of neuropathic pain associated with diabetic peripheral neuropathy, post-herpetic neuralgia, and adjunctive therapy for partial onset seizures, fibromyalgia, and neuropathic pain associated with spinal cord injury. Although the mechanism of action of pregabalin is unknown, studies in animals suggest that binding to the nervous system tissues may be involved in its pain-relieving and anti-seizure effects. Pregabalin binds with high affinity to the alpha 2-delta receptor site (a subunit of voltage-gated calcium channels) in the central nervous system. The binding of pregabalin at this site is thought to be responsible for its therapeutic effect on neuropathic pain. Reports indicate that patients are self-administering higher than recommended doses to achieve euphoria, especially patients who have a history of substance abuse, particularly opioids, and psychiatric illness. While effects of excessively high doses are generally non-lethal, gabapentinoids such as pregabalin are increasingly being identified in post-mortem toxicology analyses. Pregabalin is a Schedule V controlled substance in the United States under the CSA.

Tramadol is an opioid analgesic that produces its primary opioid-like action through an active metabolite referred to as the M1 metabolite (O-desmethyltramadol). Tramadol was first approved for marketing in the United States in 1995 and is available as immediate-release, extended-release, and combination products for the treatment of moderate to moderately severe pain. On July 2, 2014, the DEA published a final rule in the *Federal Register* controlling tramadol as a Schedule IV substance of the CSA effective from August 18, 2014. Tramadol was

pre-reviewed by the ECDD at its 28th (1992) and 32nd (2000) meetings, and critically reviewed at the 33rd (2002) meeting and not recommended for international control but placed on surveillance. Tramadol was pre-reviewed again by the ECDD at its 34th (2006) meeting; however, the ECDD concluded that there was not sufficient evidence to justify a critical review. At the 36th (2014) meeting, the ECDD considered updated information on tramadol, but again concluded that there was insufficient evidence to warrant a critical review.

Cannabidiol (CBD) is one of the active cannabinoids identified in cannabis. CBD has been shown to be beneficial in experimental models of several neurological disorders, including those of seizure and epilepsy. In the United States, CBD-containing products are in human clinical testing in three therapeutic areas, but no such products are approved by FDA for marketing for medical purposes in the United States. CBD is a Schedule I controlled substance under the CSA. At the 37th (2015) meeting of the ECDD, the committee requested that the Secretariat prepare relevant documentation to conduct pre-reviews for several substances, including CBD.

Ketamine is classified as a rapid-acting general anesthetic agent used for short diagnostic and surgical procedures that do not require skeletal muscle relaxation. It is marketed in the United States as a solution for injection. Ketamine is controlled in Schedule III of the CSA in the United States. It is not controlled internationally under the Convention on Psychotropic Substances or the Single Convention on Narcotic Drugs. The ECDD reviewed ketamine at its 34th (2006), 35th (2012), and 36th (2014) meetings. On March 13, 2015, the Commission on Narcotic Drugs (CND) decided by consensus to postpone the consideration of a proposal concerning the recommendation to place ketamine in Schedule IV of the Psychotropic Convention. The CND requested additional information from the WHO. The ECDD reviewed

updated information at its 37th (2015) meeting and found no reason to recommend a new pre-review or critical review of ketamine that could potentially change its standing 2014 recommendation that ketamine should not be placed under international control.

#### IV. Opportunity to Submit Domestic Information

As required by section 201(d)(2)(A) of the CSA, FDA, on behalf of HHS, invites interested persons to submit comments regarding the 17 named drug substances. Any comments received will be considered by HHS when it prepares a scientific and medical evaluation of these drug substances. HHS will forward a scientific and medical evaluation of these drug substances to WHO, through the Secretary of State, for WHO's consideration in deciding whether to recommend international control/decontrol of any of these drug substances. Such control could limit, among other things, the manufacture and distribution (import/export) of these drug substances and could impose certain recordkeeping requirements on them.

Although FDA is, through this notice, requesting comments from interested persons, which will be considered by HHS when it prepares an evaluation of these drug substances, HHS will not now make any recommendations to WHO regarding whether any of these drugs should be subjected to international controls. Instead, HHS will defer such consideration until WHO has made official recommendations to the Commission on Narcotic Drugs, which are expected to be made in early 2018. Any HHS position regarding international control of these drug substances will be preceded by another *Federal Register* notice soliciting public comments, as required by section 201(d)(2)(B) of the CSA.

V. Electronic Access

Persons with access to the Internet may obtain the document at either

*<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>*

or *<https://www.regulations.gov>*.

Dated: August 9, 2017.

Anna K. Abram,

Deputy Commissioner for Policy, Planning, Legislation, and Analysis.

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