



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2021-N-0739]

International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; 4F-MDMB-BICA (4F-MDMB-BUTICA); Brorphine; Metonitazene; Eutylone (bk-EBDB); BMDP (3,4-Methylenedioxy-N-benzylcathinone); Kratom (mitragynine, 7-hydroxymitragynine); Phenibut; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for comments.

SUMMARY: The Food and Drug Administration (FDA or Agency) is inviting interested persons to submit comments concerning abuse potential, actual abuse, medical usefulness, trafficking, and impact of scheduling changes on availability for medical use of seven 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 drug substances. This notice requesting comments is required by the Controlled Substances Act (CSA).

DATES: Submit either electronic or written comments by August 9, 2021.

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 August 9, 2021. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of August 9, 2021. 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-2021-N-0739 for "International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; 4F-MDMB-BICA (4F-MDMB-BUTICA); Brorphine; Metonitazene; Eutylone (bk-EBDB); BMDP (3,4-Methylenedioxy-N-benzylcathinone); Kratom (mitragynine, 7-

hydroxymitragynine); Phenibut; 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, 240-402-7500.

- 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.govinfo.gov/content/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, 240-402-7500.

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, 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 (U.N. Secretary-General) and provide the U.N. Secretary-General with information in support of its opinion.

Paragraph (d)(2)(A) 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 (nonrelevant text removed):

Ref.: C.L.20.2021

The World Health Organization (WHO) presents its compliments to Member States and Associate Members and has the pleasure of announcing that

the 44th Expert Committee on Drug Dependence (ECDD) will meet from 11 to 15 October 2021, coordinated from Geneva, Switzerland. Given that WHO Expert Committee meetings are of a closed nature, this letter serves to notify Member States of the substances under review at the 44th ECDD, which are in the Annex I, attached for reference.

WHO is mandated by the 1961 and 1971 International Drug Control Conventions to make recommendations to the UN Secretary-General on the need for and level of international control of psychoactive substances based on the advice of its independent scientific advisory body, the ECDD. To assess the appropriate control of a psychoactive substance, the ECDD convenes annually to review the potential of this substance to cause dependence, abuse and harm to health, as well as any therapeutic applications. In order to perform this review and make scientific and evidence-based decisions, the ECDD conducts medical, scientific, and public health evaluations of the selected psychoactive substances using the best available information.

Although the meetings are of a closed nature, Member States are invited to contribute to the ECDD review process by joining the 44th ECDD Open Session on 11 October 2021. The Open Session will allow interested parties to learn about present and future activities of the ECDD Secretariat, and to present information concerning substances under review to the Expert Committee. Registration information will be made available on the ECDD website: <https://www.who.int/medicines/access/controlled-substances/en/>.

As in the past and in line with the publication “*Guidance on the WHO review of psychoactive substances for international control*” (EB126/2010/REC1, Annex 6)¹, Member States can also contribute to the ECDD review process by providing accurate information concerning the substances under review in advance of the meeting. For this purpose, a questionnaire will be sent to Member States to gather country information on the legitimate use, harmful use, status of national control and potential impact of international control for each substance under evaluation.

In addition to the questionnaire, Member States are also encouraged to provide any additional relevant information (unpublished or published) on substances to be reviewed by the 44th ECDD by emailing eccdsecretariat@who.int with the subject “Ref: C.L.20.2021”.

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

GENEVA, 10 June 2021

¹ https://apps.who.int/gb/ebwha/pdf_files/EB126-REC1/B126_REC1-en.pdf#page=58.

Annex I

44th Expert Committee on Drug Dependence (ECDD)
11 - 15 October 2021, Substances For Review

Critical reviews: The substances listed below have never been formally reviewed by WHO and are not currently under international control. Information was brought to WHO's attention that these substances are clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any Party. The Expert Committee will consider whether information presented during a critical review may justify the scheduling or a change in the scheduling of the substance in the 1961 or 1971 Conventions.

Synthetic cannabinoid receptor agonists

1. 4F-MDMB-BICA (4F-MDMB-BUTICA)

Novel synthetic opioids

2. Brorphine
3. Metonitazene

Cathinones/stimulants

4. Eutylone (bk-EBDB)
5. BMDP (3,4-Methylenedioxy-N-benzylcathinone), benzylone

Pre-reviews: The substances listed below have been proposed for a pre-review. The purpose of a pre-review is to determine whether current information justifies an Expert Committee critical review. A pre-review is a preliminary analysis and findings at this stage should not determine whether the control status of a substance should be changed.

Herbal drugs

6. Kratom, mitragynine, 7-hydroxymitragynine

Medicines

7. Phenibut

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.

Access to view the WHO questionnaire can be found at <https://www.who.int/groups/who-expert-committee-on-drug-dependence/forty-fourth-ecdd-documents>.

III. Substances Under WHO Review

4F-MDMB-BICA (4F-MDMB-BUTICA) is a synthetic cannabinoid that has been sold online and used to mimic the biological effects of tetrahydrocannabinol, the main psychoactive constituent in marijuana. Research and clinical reports have demonstrated that synthetic cannabinoids are applied onto plant material so that the material may be smoked as users attempt to obtain a euphoric and psychoactive "high." Synthetic cannabinoids have been marketed under the guise of "herbal incense," and promoted by drug traffickers as legal alternatives to marijuana.

According to the National Forensic Laboratory Information System database, 4F-MDMB-BICA emerged in the United States in May 2020 through identification in drug seizures. Per NPS Discovery¹, 4F-MDMB-BICA has been identified in at least 26 toxicology cases associated with postmortem and driving under the influence of drugs investigations in the United States. There are no commercial or approved medical uses for 4F-MDMB-BICA, and it is not a controlled substance under the CSA but may be considered an analogue of other Schedule I substances.

Brorphine (chemical name: 1-(1-(1-(4-bromophenyl)ethyl)piperidin-4-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one) is a potent synthetic opioid encountered as both a single substance of abuse and in combination with other opioid substances, such as heroin and fentanyl. The appearance of brorphine on the illicit drug market is similar to other designer drugs trafficked for their psychoactive effects. Beginning in June 2019, brorphine emerged in the United States illicit, synthetic drug market as evidenced by its identification in drug seizures. The use of brorphine has been associated with at least seven fatalities between June and July 2020 in the United States. Brorphine is not approved for medical use in the United States. On March 1, 2021, the U.S. Drug Enforcement Administration issued a temporary order to control brorphine as a Schedule I substance under the CSA.

Eutylone (bk-EBDB) (chemical name: 1-(1,3-benzodioxol-5-yl)-2-(ethylamino)butan-1-one) is a designer drug of the phenethylamine class. Eutylone is a synthetic cathinone with chemical structural and pharmacological similarities to Schedule I and II amphetamines and cathinones, such as to 3,4-Methylenedioxymethamphetamine, methylone, and pentylone. Eutylone emerged in the United States illicit, synthetic drug market in 2014 as evidenced by its identification in drug seizures. Other evidence indicates that eutylone, like other Schedule I synthetic cathinones, is abused for its psychoactive effects. Adverse effects associated with synthetic cathinones abuse include agitation, hypertension, tachycardia, and death. Eutylone is

¹ <https://www.npsdiscovery.org/positivity-of-new-synthetic-cannabinoid-4f-mdmb-bica-increasing-in-u-s-as-prevalence-of-5f-mdmb-pica-wanes/>.

not approved for medical use in the United States. As a positional isomer of pentylone, eutylone is controlled in Schedule I of the CSA.

BMDP (chemical name: 3,4-Methylenedioxy-N-benzylcathinone) is a designer drug of the phenethylamine class. BMDP is a synthetic cathinone with chemical structural and pharmacological similarities to Schedule I and II amphetamines (e.g., methamphetamine and 3,4-methylenedioxymethamphetamine) and cathinones (e.g., methylone). Law enforcement has seen an increase in the encounters of BMDP in 2019 in the United States illicit, synthetic drug market as evidenced by its identification in drug seizures. BMDP has no commercial or approved medical uses, and it is not controlled under the CSA. However, if BMDP is found to meet the criteria outlined in Title 21 of the United States Code, section 802(32) (21 U.S.C. 802(32)), and it is intended for human consumption, it may be treated as a Schedule I controlled substance analogue for the purpose of Federal law pursuant to 21 U.S.C. 813.

Mitragynine and 7-hydroxymitragynine are the main active constituents of the plant *Mitragyna speciosa*, commonly known as kratom, an indigenous plant of Southeast Asia. Kratom is abused for its ability to produce opioid-like effects. Kratom is available in several different forms to include dried/crushed leaves, powder, capsules, tablets, liquids, and gum/resin. Kratom is an increasingly popular drug of abuse and readily available on the recreational drug market in the United States. Evidence suggests that kratom is abused individually and with other psychoactive substances. Kratom does not have an approved medical use in the United States and has not been studied as a treatment agent in the United States. Kratom has a history of being used as an opium substitute in Southeast Asia. In the United States, kratom is misused to self-treat chronic pain and opioid withdrawal symptoms. Consumption of kratom can lead to a number of health impacts, including, among others, respiratory depression, vomiting, nervousness, weight loss, and constipation. Kratom has been reported to have both narcotic and stimulant-like effects, and withdrawal symptoms may include hostility, aggression, excessive

tearing, aching of muscles and bones, and jerky limb movements. Kratom is not a controlled substance under the CSA.

Phenibut (chemical name: beta-phenyl-gamma-aminobutyric acid HCl) is a neuropsychotropic drug that is used in Russia to treat alcohol withdrawal, anxiety, insomnia, and vestibular disorders. It has anxiolytic and nootropic (cognition enhancing) effects. Phenibut acts as a gamma-aminobutyric acid (GABA)-mimetic, primarily at GABA(B) and, to some extent, at GABA(A) receptors. Phenibut is sold online as a supplement to improve cognitive function, memory, creativity in healthy persons, and used to self-medicate anxiety, insomnia, and alcohol cravings. There are reports of people taking phenibut arriving to emergency departments with agitation, intoxication, altered mental status, and withdrawal, and also reports of phenibut in toxicology urinalysis reports from a prison facility, where inmates were abusing multiple drugs, including phenibut. There is no approved medical use for phenibut in the United States, and phenibut is not a controlled substance under the CSA.

IV. Opportunity to Submit Domestic Information

As required by paragraph (d)(2)(A) of the CSA, FDA, on behalf of HHS, invites interested persons to submit comments regarding the 11 drug substances. Any comments received will be considered by HHS when it prepares a scientific and medical evaluation for drug substances that is responsive to the WHO Questionnaire for these drug substances. HHS will forward such evaluation of these drug substances to WHO, 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 late 2021. Any HHS position regarding international control of these drug substances will be preceded by another *Federal Register* notice soliciting public comments, as required by paragraph (d)(2)(B) of the CSA.

Dated: July 19, 2021.

Lauren K. Roth,

Acting Principal Associate Commissioner for Policy.

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