

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:**

Helena Svinglin, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 1197, Silver Spring, MD 20993-0002, 301-796-5331, [cderrdatastandards@fda.hhs.gov](mailto:cderrdatastandards@fda.hhs.gov), or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

**SUPPLEMENTARY INFORMATION:** FDA's CBER and CDER are issuing this **Federal Register** notice to announce the date that support begins for version 3.1.1 of the CDISC SENDIG and the date that this version update is required in certain submissions. The FDA guidance for industry "Providing Regulatory Submissions in Electronic Format—Standardized Study Data" (June 2021) (eStudy Data guidance), posted on FDA's Study Data Standards Resources web page at <https://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>, implements the electronic submission requirements of section 745A(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379k-1(a)) for study data contained in NDAs, ANDAs, certain BLAs, and certain INDs submitted to CDER or CBER by specifying the format for electronic submissions. The eStudy Data guidance states that a **Federal Register** notice will specify any new standards and version updates to FDA-supported study data standards that will be added to the Catalog, when the support for such standards and version updates begins or ends, and when the requirement to use such standards and version updates in submissions begins or ends.

Support for version 3.1.1 of the CDISC SENDIG begins February 15, 2022. The transition date for this version update is March 15, 2022. The requirement for electronic submissions to be submitted

using version 3.1.1 of the CDISC SENDIG is March 15, 2023, for NDAs, ANDAs, certain BLAs, and certain INDs.

Dated: February 9, 2022.

**Lauren K. Roth,**

*Associate Commissioner for Policy.*

[FR Doc. 2022-03225 Filed 2-14-22; 8:45 am]

**BILLING CODE 4164-01-P**

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. FDA-2022-N-0105]

#### International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; World Health Organization; Scheduling Recommendations; Brorphine; Metonitazene; Eutylone; Request for Comments

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is providing interested persons with the opportunity to submit written comments concerning recommendations by the World Health Organization (WHO) to impose international manufacturing and distributing restrictions, under international treaties, on certain drug substances. The comments received in response to this notice will be considered in preparing the United States' position on these proposals for a meeting of the United Nations Commission on Narcotic Drugs (CND) in Vienna, Austria, in March 2022. This notice is issued under the Controlled Substances Act (CSA).

**DATES:** Submit either electronic or written comments by February 28, 2022.

**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 February 28, 2022. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of February 28, 2022. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received 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-2022-N-0105 for "International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; World Health Organization; Scheduling Recommendations; Brorphine; Metonitazene; Eutylone; 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](mailto:james.hunter@fda.hhs.gov).

#### SUPPLEMENTARY INFORMATION:

##### I. Background

The United States is a party to the 1971 Convention on Psychotropic Substances (1971 Convention). Section 201(d)(2)(B) of the CSA (21 U.S.C. 811(d)(2)(B)) provides that when the United States is notified under Article 2 of the 1971 Convention that the CND proposes to decide whether to add a drug or other substance to one of the schedules of the 1971 Convention, transfer a drug or substance from one schedule to another, or delete it from the schedules, the Secretary of State must transmit notice of such information to the Secretary of Health and Human Services (Secretary of HHS). The Secretary of HHS must then publish

a summary of such information in the **Federal Register** and provide opportunity for interested persons to submit comments. The Secretary of HHS must then evaluate the proposal and furnish a recommendation to the Secretary of State that shall be binding on the representative of the United States in discussions and negotiations relating to the proposal.

As detailed in the following paragraphs, the Secretary of State has received notification from the Secretary-General of the United Nations (the Secretary-General) regarding one substance to be considered for control under the 1971 Convention. This notification reflects the recommendation from the 44th WHO Expert Committee for Drug Dependence (ECDD), which met in October 2021. In the **Federal Register** of July 23, 2021 (86 FR 39038), FDA announced the WHO ECDD review and invited interested persons to submit information for WHO's consideration.

The full text of the notification from the Secretary-General is provided in section II of this document. Section 201(d)(2)(B) of the CSA requires the Secretary of HHS, after receiving a notification proposing scheduling, to publish a notice in the **Federal Register** to provide the opportunity for interested persons to submit information and comments on the proposed scheduling action.

The United States is also a party to the 1961 Single Convention on Narcotic Drugs (1961 Convention). The Secretary of State has received a notification from the Secretary-General regarding two substances to be considered for control under this convention. The CSA does not require HHS to publish a summary of such information in the **Federal Register**. Nevertheless, to provide interested and affected persons an opportunity to submit comments regarding the WHO recommendations for drugs under the 1961 Convention, the notification regarding these substances is also included in this **Federal Register** notice. The comments will be shared with other relevant Agencies to assist the Secretary of State in formulating the position of the United States on the control of these substances. The HHS recommendations are not binding on the representative of the United States in discussions and negotiations relating to the proposal regarding control of substances under the 1961 Convention.

##### II. United Nations Notification

The formal notification from the United Nations that identifies the drug substances and explains the basis for the

scheduling recommendations is reproduced as follows (non-relevant text removed):

#### Reference:

NAR/CL.13/2021

WHO/ECDD44; 1961C-Art.3, 1971C-Art.2  
CU 2021/453/DTA/SGB

The Secretariat of the United Nations presents its compliments to the Permanent Mission of the United States of America and has the honour to inform the Government that in a letter dated 18 November 2021, the Director-General of the World Health Organization (WHO), pursuant to article 3, paragraphs 1 and 3 of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol (1961 Convention), and article 2, paragraphs 1 and 4 of the Convention on Psychotropic Substances of 1971 (1971 Convention), notified the Secretary-General of the following recommendations of the forty-third Meeting of the WHO's Expert Committee on Drug Dependence (ECDD):

*Substance recommended to be added to Schedule I of the 1961 Convention:*

—Brophine

*IUPAC (International Union of Pure and Applied Chemistry) name:* 1-[1-[4-(Bromophenyl)ethyl]-piperidin-4-yl]-1,3-dihydro-2H-imidazol-2-one

—Metonitazene

*IUPAC name:* N,N-Diethyl-2-(2-(4-methoxybenzyl)-5-nitro-1H-benzo[d]imidazol-1-yl)ethan-1-amine  
*Substances recommended to be added to Schedule II of the 1971 Convention:*

—Eutylone (*alternate name:* 3,4-methylenedioxy- $\alpha$ -ethylamino butiophenone)

*IUPAC names:* 1-(Benzo[d][1,3]dioxol-5-yl)-2-(ethylamino)butan-1-one 1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)butan-1-one

*Substances to be kept under surveillance:*

In the letter from the Director-General of WHO to the Secretary-General, reference is also made to the recommendation made by the WHO Expert Committee on Drug Dependence (ECDD), at its forty-fourth meeting, to keep the following substances under surveillance:

—4F-MDMB-BICA (*alternate name:* 4F-MDMB-BUTICA)

*IUPAC names:* Methyl 2-([1-(4-fluorobutyl)-1H-indol-3-yl]carbonyl)amino-3,3-dimethylbutanoate; Methyl 2-(1-(4-fluorobutyl)-1H-indole-3-carboxamido)-3,3-dimethylbutanoate

—Benzylone (*alternate name:* 3,4-Methylenedioxy-N-benzylcathinone)

*IUPAC name:* 1-(Benzo[d][1,3]dioxol-5-yl)-2-(benzylamino)propan-1-one

—Kratom, mitragynine, and 7-hydroxymitragynine

—Phenibut (*alternate name:* 4-amino-3-phenyl-butyric acid)

*IUPAC name:* 4-Amino-3-phenylbutanoic acid

In accordance with the provisions of article 3, paragraph 2, of the 1961 Convention and article 2, paragraph 2, of the 1971 Convention, the notification is hereby transmitted as annex I to the present note. In connection with the notification, WHO also submitted a summary of the assessments and

findings for these recommendations made by ECDD, which is transmitted as annex II.

Also, in accordance with the same provisions, the notification from WHO will be brought to the attention of the sixty-fifth session of the Commission on Narcotic Drugs (14–18 March 2022, tent.) in a pre-session document that will be made available in the six official languages of the United Nations on the website of the 65th session of the Commission on Narcotic Drugs: [https://www.unodc.org/unodc/en/commissions/CND/session/65\\_Session\\_2022/65CND\\_Main.html](https://www.unodc.org/unodc/en/commissions/CND/session/65_Session_2022/65CND_Main.html).

In order to assist the Commission in reaching a decision, it would be appreciated if the Permanent Mission could communicate any comments it considers relevant to the possible scheduling of substances recommended by WHO to be placed under international control under the 1961 Convention, namely:

—Borophine

—Metonitazene; as well as any economic, social, legal, administrative or other factors that it considers relevant to the possible scheduling of substances recommended by WHO to be placed under international control under the 1971 Convention, namely:

—Eutylone (*alternate name*: 3,4-methylenedioxy- $\alpha$ -ethylamino butiophenone).

The Secretariat of the United Nations avails itself of this opportunity to renew to the Permanent Mission of the United States of America to the United Nations (Vienna) the assurances of its highest consideration. 8 December 2021

#### Annex I

*Letter addressed to the Secretary-General of the United Nations from the Director-General of the World Health Organization, dated 18 November 2021*

“The Forty-fourth Meeting of the World Health Organization (WHO)’s Expert Committee on Drug Dependence (ECDD) was convened in a virtual format from 11 to 15 October 2021 and was coordinated from the WHO headquarters in Geneva.

WHO is mandated by the 1961 and 1971 International Drug Control Conventions to make recommendations to the United Nations 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. In order to recommend if a psychoactive substance should be placed under international control or if its level of control should be changed, the WHO convenes the ECDD annually to thoroughly review the potential for abuse, dependence, and harm to health of a psychoactive substance, as well as any therapeutic applications.

The Forty-fourth WHO ECDD Meeting critically reviewed five new psychoactive substances, including one synthetic cannabinoid receptor agonist (4F-MDMB-BICA), two novel synthetic opioids (borophine; metonitazene), and two cathinones/stimulants (eutylone; benzylone). These substances had not previously been formally reviewed by WHO and are currently

not 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 recognised therapeutic use by any Party. Therefore, a critical review to consider international scheduling measures was undertaken for each substance so that the Expert Committee could consider whether information available about these substances may justify the scheduling or a change in scheduling of a substance in the 1961 or 1971 Conventions.

In addition, the Forty-fourth ECDD Meeting carried out pre-reviews of kratom, mitragynine, and 7-hydroxymitragynine; and phenibut to consider whether current information justified a critical review.

With reference to Article 3, paragraphs 1 and 3 of the Single Convention on Narcotic Drugs (1961), as amended by the 1972 Protocol, and Article 2, paragraphs 1 and 4 of the Convention on Psychotropic Substances (1971), WHO is pleased to endorse and submit the following recommendations of the Forty-fourth Meeting of the ECDD:

*To be added to Schedule I of the Single Convention on Narcotic Drugs (1961):*

—Borophine

*IUPAC (International Union of Pure and Applied Chemistry) name*: 1-[1-[1-(4-Bromophenyl)ethyl]-piperidin-4-yl]-1,3-dihydro-2H-imidazol-2-one

—Metonitazene

*IUPAC name*: N,N-Diethyl-2-(2-(4-methoxybenzyl)-5-nitro-1H-benzo[d]imidazol-1-yl)ethan-1-amine

*To be added to Schedule II of the Convention on Psychotropic Substances (1971):*

—Eutylone (*alternate name*: 3,4-methylenedioxy- $\alpha$ -ethylamino butiophenone)

*IUPAC names*: 1-(Benzo[d][1,3]dioxol-5-yl)-2-(ethylamino)butan-1-one; 1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)butan-1-one

*To be kept under surveillance:*

—4F-MDMB-BICA (*alternate name*: 4F-MDMB-BUTICA)

*IUPAC names*: Methyl 2-([1-(4-fluorobutyl)-1H-indol-3-yl]carbonyl)amino)-3,3-dimethylbutanoate; Methyl 2-(1-(4-fluorobutyl)-1H-indole-3-carboxamido)-3,3-dimethylbutanoate

—Benzylone (*alternate name*: 3,4-

Methylenedioxy-N-benzylcathinone)

*IUPAC name*: 1-(Benzo[d][1,3]dioxol-5-yl)-2-(benzylamino)propan-1-one

—Kratom, mitragynine, 7-

hydroxymitragynine

—Phenibut (*alternate name*: 4-amino-3-phenyl-butyric acid)

*IUPAC name*: 4-Amino-3-phenylbutanoic acid

The assessments and findings on which these recommendations are based are set out in detail in the Forty-fourth ECDD Meeting Report of the WHO Expert Committee on Drug Dependence. A summary of the assessments and findings for these recommendations made by the ECDD is contained in Annex 1 to this letter.

I am very pleased with the ongoing collaboration between WHO, the United

Nations Office on Drugs and Crime and the International Narcotics Control Board, and in particular, how this collaboration has benefited the work of the WHO Expert Committee on Drug Dependence and more generally, the implementation of the operational recommendations of the United Nations General Assembly Special Session 2016.”

#### Annex II

*Summary assessment and recommendations of the 44th Expert Committee on Drug Dependence, 11–15 October 2021*

*Substances to be added to Schedule I of the Single Convention on Narcotic Drugs (1961):*

Borophine

Substance Identification

Borophine (*IUPAC chemical name*: 1-[1-[1-(4-bromophenyl)ethyl]-piperidin-4-yl]-1,3-dihydro-2H-imidazol-2-one) has a chemical structure similar to bezitramide, an opioid listed in Schedule I of the 1961 Convention. Borophine freebase has been described as a white or off-white solid, and the hydrochloride salt as a neat solid, with seized samples described as white, yellowish, gray, purple, or white powder, or in crystal form. It is also found in tablets and capsules as falsified opioid medicines. It is reported to be used by the oral, inhalation, and intravenous routes of administration.

WHO Review History

Borophine has not been formally reviewed by WHO and is not currently under international control. Information was brought to WHO’s attention that this substance is manufactured clandestinely, poses a risk to public health, and is of no recognized therapeutic use.

Similarity to Known Substances and Effects on Central Nervous System

Borophine is a full agonist at the  $\mu$ -opioid receptor, with greater potency than morphine, and less potency than fentanyl. It has analgesic effects that are reversed by an opioid antagonist and, based on its mechanism of action, it would be expected to produce other typical opioid effects such as respiratory depression and sedation. Borophine may be convertible to bezitramide, which is an opioid listed in Schedule I of the 1961 Single Convention on Narcotic Drugs.

Dependence Potential

No controlled animal or human studies have examined the dependence potential of borophine. As a potent  $\mu$ -opioid agonist, it would be expected to produce dependence similar to other opioid substances. Unverified online reports describe tolerance and withdrawal following repeated borophine use.

Actual Abuse and/or Evidence of Likelihood of Abuse

In an animal model predictive of abuse potential, borophine was shown to produce effects similar to morphine and fentanyl.

Deaths involving borophine have been reported in several countries. Deaths commonly occur after use of borophine in

combination with other opioids or with benzodiazepines such as flualprazolam. Brorphine has been identified in falsified opioid medicines, suggesting that sometimes its use may be unintentional. Fatal and non-fatal intoxications due to brorphine share features with intoxications due to other opioids, such as pulmonary oedema. Brorphine has been detected with other substances in biological fluids in cases of driving under the influence.

Seizures have been reported in multiple countries and regions.

#### Therapeutic Usefulness

Brorphine is not known to have any therapeutic use.

#### Recommendation

The mechanism of action of brorphine indicates that it is liable to have similar abuse potential and ill effects as opioids that are controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs.

Its use has been reported in a number of countries and has been associated with adverse effects, including death. It has no known therapeutic use and is likely to cause substantial harm.

**Recommendation:** The Committee recommended that brorphine (*IUPAC chemical name:* 1-[1-(4-bromophenyl)ethyl]-piperidin-4-yl]-1,3-dihydro-2H-imidazol-2-one) be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

#### Metonitazene

##### Substance Identification

Metonitazene (*IUPAC chemical name:* *N,N*-Diethyl-2-(2-(4-methoxybenzyl)-5-nitro-1*H*-benzo[d]imidazol-1-yl)ethan-1-amine) belongs to the series of 2-benzylbenzimidazole opioid compounds. It is a white or off-white/beige or coloured powder, and is sometimes crystalline in consistency. Reports suggest that it is used intranasally and by intravenous injection.

##### WHO Review History

Metonitazene has not been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is manufactured clandestinely, poses a risk to public health, and has no recognized therapeutic use.

##### Similarity to Known Substances and Effects on Central Nervous System

Metonitazene is a chemical analogue of etonitazene and isotonitazene, both of which are Schedule I compounds under the Single Convention on Narcotic Drugs, 1961. Metonitazene is a potent opioid analgesic with a rapid onset of action and greater potency than fentanyl and hydromorphone. Limited early clinical research demonstrated that metonitazene produces analgesia and typical opioid adverse effects including sedation, respiratory depression, nausea, and vomiting. The effects of metonitazene have been shown to be reversed by an opioid antagonist.

##### Dependence Potential

Animal studies have demonstrated that metonitazene suppresses opioid withdrawal

and has potent  $\mu$ -opioid agonist effects. No controlled human studies have reported on the dependence potential of metonitazene, but as a potent  $\mu$ -opioid agonist, it would be expected to produce dependence similar to other opioids.

##### Actual Abuse and/or Evidence of Likelihood of Abuse

No controlled studies have been reported on the abuse potential of metonitazene, but as it is a potent  $\mu$ -opioid receptor agonist, it would be expected to have high abuse liability. Online reports from people who report use of metonitazene describe its euphoric and opioid-like effects.

A number of deaths have been reported in association with use of metonitazene. In many of these cases metonitazene has been used in combination with other opioids or benzodiazepines. However, in some fatalities, metonitazene was the sole substance identified in the analyzed biological samples.

Trafficking and use of metonitazene have been reported from a number of countries across several regions.

##### Therapeutic Usefulness

Metonitazene is not known to have any therapeutic use.

##### Recommendation

The mechanism of action and effects of metonitazene indicate that it is liable to have similar abuse potential and ill effects as opioids that are controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs. Its use has been reported in a number of countries and been associated with adverse effects, including death. Metonitazene has no known therapeutic use and is likely to cause substantial harm.

**Recommendation:** The Committee recommended that metonitazene (*IUPAC chemical name:* *N,N*-Diethyl-2-(2-(4-methoxybenzyl)-5-nitro-1*H*-benzo[d]imidazol-1-yl)ethan-1-amine) be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

**Substances to be added to Schedule II of the Convention on Psychotropic Substances (1971):**

Eutylone (3,4-methylenedioxy- $\alpha$ -ethylamino butiophenone)

##### Substance Identification

Eutylone (*IUPAC chemical name:* 1-(Benzo[d][1,3]dioxol-5-yl)-2-(ethylamino)butan-1-one) is a synthetic cathinone of the phenethylamine class. The hydrochloride salt of eutylone has been described as a crystalline solid. Eutylone is mostly found as tablets, capsules, and crystals. It is used orally and intranasally.

##### WHO Review History

Eutylone has not been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is manufactured clandestinely, poses a risk to public health, and has no recognized therapeutic use.

##### Similarity to Known Substances and Effects on Central Nervous System

Eutylone is a synthetic cathinone with a mechanism of action and effects similar to

other cathinones and to stimulants such as methamphetamine. Related cathinones, such as methylone and *N*-ethylnorpentylone, are listed under Schedule II of the Convention on Psychotropic Substances of 1971. The clinical features described are similar to other cathinones, including sympathomimetic effects and psychostimulant effects such as euphoria, insomnia, tachycardia, agitation, anxiety, delirium and psychosis.

##### Dependence Potential

No animal or human studies have been conducted on the dependence potential of eutylone. Based on its overall profile of effects, eutylone would be expected to produce dependence similar to other psychostimulants.

##### Actual Abuse and/or Evidence of Likelihood of Abuse

In an animal model predictive of abuse potential, eutylone has been shown to produce effects similar to those of methamphetamine. Online reports from people reporting use of eutylone suggest that it has high abuse potential.

Eutylone has been detected in biological samples from forensic, post-mortem, and driving under the influence cases. Published case reports describe fatalities as a result of eutylone use. In addition to the effects described above, reported adverse events in these cases have included rhabdomyolysis, hyperthermia, hypertension, and seizures.

Eutylone has been detected in seized materials in multiple countries across several regions.

##### Therapeutic Usefulness

Eutylone is not known to have any therapeutic use.

##### Recommendation

Eutylone has effects similar to those of related cathinones listed under Schedule II of the Convention on Psychotropic Substances of 1971.

There is evidence that this substance is used in multiple countries in various regions. Eutylone causes substantial harm, including severe adverse events and fatal intoxications. Its mode of action suggests a likelihood of abuse and it poses a substantial risk to public health. It has no known therapeutic usefulness.

**Recommendation:** The Committee recommended that eutylone (*IUPAC chemical name:* 1-(Benzo[d][1,3]dioxol-5-yl)-2-(ethylamino)butan-1-one) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

**Substances to be kept under surveillance:**

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

##### Substance Identification

4F-MDMB-BICA (*IUPAC chemical name:* Methyl 2-([1-(4-fluorobutyl)-1*H*-indol-3-yl]carbonyl)amino)-3,3-dimethylbutanoate) has a chemical structure similar to a number of synthetic cannabinoids. It has been identified in seized materials as a white, off-white, brown or orange powder, and has been identified in herbal blends, vaping solutions, and infused onto paper. It is also available as a reference material as crystalline solid.

## WHO Review History

4F-MDMB-BICA has not been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is manufactured clandestinely, poses a risk to public health, and has no recognized therapeutic use.

## Similarity to Known Substances and Effects on Central Nervous System

4F-MDMB-BICA is a synthetic cannabinoid, structurally related to 5F-MDMB-PICA, a synthetic cannabinoid, which is included in Schedule II of the United Nations Single Convention on Psychotropic Substances of 1971. Some data suggest that 4F-MDMB-BICA has activity at the cannabinoid CB1 receptor, but this action may not be identical to that exerted by other CB1 agonists. No animal or human studies have evaluated the effects of 4F-MDMB-BICA, and there is insufficient data on 4F-MDMB-BICA overdose cases to confirm that it has typical cannabinoid effects.

## Dependence Potential

No studies have been reported in animals or humans on the dependence potential of 4F-MDMB-BICA.

## Actual Abuse and/or Evidence of Likelihood of Abuse

No studies have been reported in animals or humans to indicate the likelihood of abuse of 4F-MDMB-BICA. A number of countries in various regions have reported use of 4F-MDMB-BICA. Its use has been associated with multiple deaths and Emergency Department visits, although multiple substances have been present in analysed biological samples, and the relationship between 4F-MDMB-BICA exposure and cause of death is not established.

## Therapeutic Usefulness

4F-MDMB-BICA is not known to have any therapeutic use.

## Recommendation

4F-MDMB-BICA has a structure similar to other synthetic cannabinoids, but its mechanism of action has yet to be confirmed. The magnitude of harm due to 4F-MDMB-BICA alone is unclear, and no animal or human studies have examined the effects or abuse potential of 4F-MDMB-BICA. Based on the limited information available concerning abuse, dependence and risks to public health, there is insufficient evidence to justify placing 4F-MDMB-BICA under international control.

**Recommendation:** The Committee recommended that 4F-MDMB-BICA (*IUPAC chemical name:* Methyl 2-((1-(4-fluorobutyl)-1*H*-indol-3-yl)carbonyl)amino)-3,3-dimethylbutanoate) be kept under surveillance by the WHO Secretariat.

Benzylone (3,4-Methylenedioxy-N-benzylcathinone)

## Substance Identification

Benzylone (*IUPAC chemical name:* 1-(Benzo[d][1,3]dioxol-5-yl)-2-(benzylamino)propan-1-one) is a ring-substituted synthetic cathinone. Benzylone is a white powder. The hydrochloride salt of benzylone is a crystalline solid.

## WHO Review History

Benzylone has not been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is manufactured clandestinely, poses a risk to public health, and has no recognized therapeutic use.

## Similarity to Known Substances and Effects on Central Nervous System

Benzylone has a mode of action suggestive of stimulant effects similar to other cathinones. However, these effects are relatively weak and it fails to produce stimulant effects in animal models.

Limited information is available on its effects in humans.

## Dependence Potential

There is no information available on the dependence potential of benzylone in animals or humans

## Actual Abuse and/or Evidence of Likelihood of Abuse

In an animal model predictive of abuse potential, benzylone did not produce effects similar to MDMA, and its similarity to methamphetamine is unclear. No human studies have been conducted to assess abuse liability.

Benzylone has been detected in seized materials in multiple countries across several regions.

There is little information concerning the adverse effects of benzylone. Although it has been detected in postmortem samples along with other substances, there is no significant evidence of benzylone playing a causative role in deaths.

## Therapeutic Usefulness

Benzylone is not known to have any therapeutic use.

## Recommendation

Benzylone is a synthetic cathinone that has some effects in common with substances listed under Schedule II of the Convention on Psychotropic Substances of 1971. However, its effects are relatively weak and there is no consistent evidence supporting the likelihood of abuse or dependence. In addition, there is no consistent evidence of the extent of public health and social problems related to use of benzylone.

**Recommendation:** The Committee recommended that benzylone (*IUPAC chemical name:* 1-(Benzo[d][1,3]dioxol-5-yl)-2-(benzylamino)propan-1-one) be kept under surveillance by the WHO Secretariat.

Kratom, mitragynine, and 7-hydroxymitragynine

## Substance Identification

Kratom is the common term for *Mitragyna speciosa*, a tree native to Southeast Asia. Kratom use is almost exclusively oral, typically by chewing the leaves, ingesting powdered leaf, or drinking a kratom infusion or decoction, or by ingesting powdered leaf as a capsule or pill or dissolved in a beverage. Other forms such as extracts and resins are also used.

Several alkaloids have been detected in kratom plants. The main known psychoactive

components of kratom are mitragynine and 7-hydroxymitragynine, both of which are found in the leaves of *Mitragyna speciosa*. Mitragynine is the most abundant alkaloid in kratom.

Whilst 7-hydroxymitragynine is a minor alkaloid, it is also a metabolite of mitragynine.

## WHO Review History

Kratom has been under ECDD surveillance since 2020 due to a country level report indicating the potential for abuse, dependence, and harm to public health from mitragynine and 7-hydroxymitragynine, and a report from an international organization regarding documented fatalities associated with kratom use. A pre-review on kratom, mitragynine, and 7-hydroxymitragynine was initiated following consideration of these reports.

## Similarity to Known Substances and Effects on Central Nervous System

Mitragynine and 7-hydroxymitragynine are partial agonists at the mu-opioid receptor. Human studies demonstrate the analgesic effects of kratom, while kratom extract, mitragynine and 7-hydroxymitragynine have been shown to be antinociceptive in animal models. The antinociceptive effects are reversed by an opioid antagonist.

Mitragynine also binds to adrenergic receptors, serotonergic and dopamine receptors. Although there is limited information regarding its effects at these receptors, kratom extracts and mitragynine have been reported in animal studies to have a variety of non-opioid-like behavioural effects, including antidepressant and antipsychotic effects.

Reported adverse effects as a result of kratom intoxication have included neuropsychiatric (agitation, confusion, sedation, hallucinations, tremor, seizure, coma), cardiovascular (tachycardia, hypertension), gastrointestinal (abdominal pain, nausea, vomiting) and respiratory (respiratory depression) symptoms. A number of cases of kratom-associated liver toxicity have been documented.

## Dependence Potential

In animal models, repeated dosing with mitragynine produced dependence, evidenced by naloxone-precipitated withdrawal. The withdrawal syndrome from kratom appears to be less severe than withdrawal from morphine.

In humans, opioid-like withdrawal symptoms have been reported following cessation of kratom use. Limited epidemiological evidence indicates that withdrawal is usually mild. There are a small number of cases of neonatal opioid withdrawal symptoms in neonates born to mothers who used kratom regularly.

## Actual Abuse and/or Evidence of Likelihood of Abuse

Animal studies with kratom extracts have not shown abuse liability in one animal model. Mitragynine and 7-hydroxymitragynine have effects indicative of abuse liability in some animal models but not in others. Mitragynine is not self-administered by animals, while 7-hydroxymitragynine has been shown to be

self-administered, supporting a likely abuse liability.

Kratom can produce serious toxicity in people who use high doses, but the number of cases is probably low as a proportion of the total number of people who use kratom. Although mitragynine has been analytically confirmed in a number of deaths, almost all involve use of other substances, so the degree to which kratom use has been a contributory factor to fatalities is unclear.

Kratom and mitragynine have been associated with cases of driving under the influence, but their role in driving impairment could not be established in most instances.

Multiple countries across various regions report nonmedical use of kratom. Seizures of kratom and related products have been reported in several countries.

#### Therapeutic Usefulness

People report using kratom to self-medicate a variety of disorders and conditions, including pain, opioid withdrawal, opioid use disorder, anxiety, and depression. Kratom is being used as a part of traditional medicine in some countries.

Research is ongoing to determine the basic pharmacology and the potential therapeutic value of kratom, mitragynine, and 7-hydroxymitragynine.

#### Recommendation

Kratom contains multiple alkaloids. The two main known psychoactive alkaloids, mitragynine and 7-hydroxymitragynine, produce at least some effects similar to opioids under international control.

Mitragynine, the most abundant of these alkaloids, also has non-opioid actions, the significance of which is unclear. There is mixed evidence on the abuse liability of mitragynine in animal models. Kratom is used for self-medication for a variety of disorders but there is limited evidence of abuse liability in humans.

Cessation of regular use of kratom may lead to withdrawal symptoms.

The Committee considered information regarding the traditional use and investigation into possible medical applications of kratom.

The Committee concluded that there is insufficient evidence to recommend a critical review of kratom. With respect to mitragynine and 7-hydroxymitragynine, the Committee, except for one member, also concluded that there is insufficient evidence to recommend a critical review at this time.

**Recommendation:** The Committee recommended that kratom, mitragynine, and 7-hydroxymitragynine be kept under surveillance by the WHO Secretariat.

Phenibut (4-amino-3-phenyl-butyric acid)

#### Substance Identification

Phenibut (*IUPAC chemical name:* 4-Amino-3-phenylbutanoic acid) is a structural analogue of baclofen and gabapentin. It is produced in various formulations including tablets and powder for oral use, and crystalline form. Phenibut is a registered pharmaceutical in some countries and is also marketed online for a number of uses including as a sleep aid, mood enhancer,

treatment for anxiety and a cognitive enhancer.

#### WHO Review History

Phenibut has not been formally reviewed by WHO and is not currently under international control. Phenibut has been under ECDD surveillance since 2017 due to reports from Member States of its abuse and dependence potential. A pre-review was initiated following consideration of these reports.

#### Similarity to Known Substances and Effects on Central Nervous System

Phenibut acts primarily as an agonist at the GABA<sub>B</sub> receptor, similar to baclofen, and at the  $\alpha 2$ - $\delta$  subunit of voltage dependent calcium channels, similar to gabapentin.

Animal studies show that phenibut has dose-dependent analgesic, antidepressant, and anxiolytic effects, which are mediated both by its GABA<sub>B</sub> agonist effects and actions at voltage dependent calcium channels.

Phenibut intoxication has presented with central nervous system depressive symptoms including decreased level of consciousness, muscle tone, stupor, depressed respiration, temperature dysregulation, hyper- or hypotension, and coma. However, in other cases individuals have presented with agitation, hallucinations, seizures, and delirium.

#### Dependence Potential

There are no studies conducted in animals examining the dependence potential of phenibut. People who use phenibut describe escalating dosing suggestive of tolerance and difficulty in cessation.

There are a limited number of case reports of withdrawal symptoms following abrupt discontinuation of high dose phenibut use. Reported symptoms have included insomnia, psychomotor agitation, delusions, psychosis, disorganized thought patterns, auditory/visual hallucinations, anxiety, depression, fatigue, dizziness, seizures, decreased appetite, nausea and vomiting, palpitations, and tachycardia. However, in most cases the use of phenibut was not verified analytically, and the clinical picture was complicated by the use of other drugs.

#### Actual Abuse and/or Evidence of Likelihood of Abuse

No controlled animal or human studies have examined the abuse potential of phenibut.

There are reports from different countries of adverse effects due to nonmedical use of phenibut. Medically unsupervised use of phenibut obtained via the internet is often at doses much higher than those used clinically. However, many cases involve multiple drugs, and the role of phenibut in these cases remains unclear.

Multiple countries over several regions report seizures of phenibut. However, the extent of non-medical use is unknown.

#### Therapeutic Usefulness

Phenibut is approved in a few countries as a medicine for a range of psychiatric and neurological conditions.

#### Recommendation

The Committee noted that there has been concern in several countries regarding the

nonmedical use of phenibut. While there are reports of adverse effects and of a withdrawal syndrome following cessation of use, the information on these cases is very limited. In addition, there is very little information on the abuse liability of phenibut, on the magnitude of its misuse or abuse, and on its similarity to currently internationally controlled substances.

The Committee also noted that phenibut is used therapeutically in a small number of countries.

**Recommendation:** The Committee recommended that phenibut (*IUPAC chemical name:* 4-Amino-3-phenylbutanoic acid) should not proceed to critical review but should be kept under surveillance by the WHO Secretariat.

### III. Discussion

Although WHO has made specific scheduling recommendations for each of the drug substances, the CND is not obliged to follow the WHO recommendations. Options available to the CND for substances considered for control under the 1971 Convention include the following: (1) Accept the WHO recommendations; (2) accept the recommendations to control but control the drug substance in a schedule other than that recommended; or (3) reject the recommendations entirely.

Borophine (*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 borophine on the illicit drug market is similar to other designer drugs trafficked for their psychoactive effects. Beginning in June 2019, borophine emerged in the United States illicit, synthetic drug market as evidenced by its identification in drug seizures. The use of borophine has been associated with at least seven fatalities between June and July 2020 in the United States. Borophine is not approved for medical use in the United States. On March 1, 2021, the U.S. Drug Enforcement Administration (DEA) issued a temporary order to control borophine as a Schedule I substance under the CSA, therefore additional permanent controls may be needed if borophine is placed in Schedule I of the 1961 Convention.

Metonitazene (*chemical name:* N,N-diethyl-2-(2-(4-methoxybenzyl)-5-nitro-1H-benzo[d]imidazol-1-yl)ethan-1-amine) belongs to the series of 2-benzylbenzimidazole opioid compounds and is classified as a potent opioid structurally resembling etonitazene and dissimilar in structure to other synthetic opioids such as fentanyl analogues. Novel opioids such as metonitazene have been reported to

cause psychoactive effects and adverse events, including deaths similar to heroin, fentanyl, and other opioids. As of January 2021, metonitazene has been identified in eight blood specimens associated with postmortem death investigations in the United States. There are no commercial or approved medical uses for metonitazene. On December 7, 2021, the DEA issued a temporary order (86 FR 69182) to control metonitazene as a Schedule I substance under the CSA, therefore additional permanent controls may be needed if metonitazene is placed in Schedule I of the 1961 Convention.

Eutylone (*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 not approved for medical use in the United States. As a positional isomer of pentylone, eutylone is controlled in Schedule I of the CSA. As such, additional permanent controls will not be needed if eutylone is placed in Schedule II of the Convention on Psychotropic Substances.

FDA, on behalf of the Secretary of HHS, invites interested persons to submit comments on the notifications from the United Nations concerning these drug substances. FDA, in cooperation with the National Institute on Drug Abuse, will consider the comments on behalf of HHS in evaluating the WHO scheduling recommendations. Then, under section 201(d)(2)(B) of the CSA, HHS will recommend to the Secretary of State what position the United States should take when voting on the recommendations for control of substances under the 1971 Convention at the CND meeting in March 2022.

Comments regarding the WHO recommendations for control of bupropion and metonitazene under the 1961 Single Convention will also be forwarded to the relevant Agencies for consideration in developing the U.S.

position regarding narcotic substances at the CND meeting.

Dated: February 9, 2022.

**Lauren K. Roth,**

*Associate Commissioner for Policy.*

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

**[Docket Nos. FDA–2010–D–0575 and FDA–2021–N–0764]**

#### **Compliance Policy Guide Sec. 510.800 Beverages—Serving Size Labeling; Compliance Policy Guide Sec. 540.420 Raw Breaded Shrimp—Microbiological Criteria for Evaluating Compliance With Current Good Manufacturing Practice Regulations; and Compliance Policy Guide Sec. 562.800 Vending Machine Food—Labeling; Withdrawal of Guidances**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice; withdrawal.

**SUMMARY:** The Food and Drug Administration (FDA or we) is announcing the withdrawal of three compliance policy guides (CPG) entitled “Compliance Policy Guide Sec. 510.800 Beverages—Serving Size Labeling,” “Compliance Policy Guide Sec. 540.420 Raw Breaded Shrimp—Microbiological Criteria for Evaluating Compliance with Current Good Manufacturing Practice Regulations,” and “Compliance Policy Guide Sec. 562.800 Vending Machine Food—Labeling.” We are withdrawing these CPGs because they have become outdated or have been superseded by subsequent FDA actions.

**DATES:** The withdrawal is applicable February 15, 2022.

**ADDRESSES:** For access to the docket, go to <https://www.regulations.gov> and insert docket number FDA–2010–D–0575 for “Compliance Policy Guide Sec. 510.800 Beverages—Serving Size Labeling” or FDA–2021–N–0764 for “Compliance Policy Guide Sec. 540.420 Raw Breaded Shrimp—Microbiological Criteria for Evaluating Compliance with Current Good Manufacturing Practice Regulations” and “Compliance Policy Guide Sec. 562.800 Vending Machine Food—Labeling” 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:** Kevin Kwon, Office of Compliance

(HFS–605), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, 240–402–4597; or Alexandra Jurewitz, Office of Regulations and Policy (HFS–024), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, 240–402–2378.

#### **SUPPLEMENTARY INFORMATION:**

##### **I. Background**

We are announcing the withdrawal of three CPGs entitled “Compliance Policy Guide Sec. 510.800 Beverages—Serving Size Labeling,” “Compliance Policy Guide Sec. 540.420 Raw Breaded Shrimp—Microbiological Criteria for Evaluating Compliance with Current Good Manufacturing Practice Regulations,” and “Compliance Policy Guide Sec. 562.800 Vending Machine Food—Labeling.”

CPG Sec. 510.800 entitled “Beverages—Serving Size Labeling” was first issued in December 2010. This CPG provided guidance for FDA staff and industry as to when we would typically consider not taking enforcement action in connection to a “12 [fluid ounce] (360 [milliliter])” labeled serving size on specific types of beverages larger than 20 fluid ounces. On May 27, 2016, FDA issued a final rule entitled “Food Labeling: Serving Sizes of Foods That Can Reasonably Be Consumed at One Eating Occasion; Dual-Column Labeling; Updating, Modifying, and Establishing Certain Reference Amounts Customarily Consumed; Serving Size for Breath Mints; and Technical Amendments” (81 FR 34000). The final rule amended the Reference Amounts Customarily Consumed (RACCs) that are used by manufacturers to determine serving sizes for certain foods, including certain beverages. Our regulations, at 21 CFR 101.12(b), table 2, lists the categories for each type of food product and each category’s current RACC. Due to the updated RACCs for certain beverages, CPG Sec. 510.800 is now obsolete, and the enforcement discretion provided in this CPG is no longer applicable. Therefore, CPG Sec. 510.800 is being withdrawn.

CPG Sec. 540.420 entitled “Raw Breaded Shrimp—Microbiological Criteria for Evaluating Compliance with Current Good Manufacturing Practice Regulations” was first issued in August 1983. This CPG used data collected in fiscal year 1978 and listed an outdated sampling and compliance structure. The compliance criteria and the methodology used in the CPG have become outdated and are no longer useful. This CPG is superseded by the