1/11/22

The following information is being provided pursuant to the requirements of Executive Order 2011-01K and Senate Bill 2 of the 129th General Assembly, which require state agencies, including the State of Ohio Board of Pharmacy, to draft rules in collaboration with stakeholders, assess and justify an adverse impact on the business community (as defined by S.B. 2), and provide an opportunity for the affected public to provide input on the following rule.

Amend:

- 4729:9-1-01 – Updates the incorporation by reference to the temporary federal schedules. Adds the following compounds as schedule I controlled substances:
    - 2-Methyl-AP-237 (1-[2-methyl-4-[(E)-3-phenylprop-2-enyl]piperazin-1-yl]butan-1-one).
    - AP-237 (1-[4-(3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone).

Comments on the proposed rule will be accepted until close of business on **January 25, 2022**. Please send all comments to the following email address: RuleComments@pharmacy.ohio.gov

In addition, please copy your comments to: CSIPublicComments@governor.ohio.gov

Business Impact Analysis

Agency, Board, or Commission Name: State of Ohio Board of Pharmacy

Rule Contact Name and Contact Information: Cameron McNamee
Cameron.mcnamee@pharmacy.ohio.gov

Regulation/Package Title (a general description of the rules' substantive content):

Schedule I Controlled Substances

Rule Number(s): 4729:9-1-01

Date of Submission for CSI Review: 1/11/22

Public Comment Period End Date: 1/25/22

Rule Type/Number of Rules:

New/ ___ rules
Amended/ 1 rules (FYR? Y)
No Change/___ rules (FYR? __)
Rescinded/____ rules (FYR? ___)

The Common Sense Initiative is established in R.C. 107.61 to eliminate excessive and duplicative rules and regulations that stand in the way of job creation. Under the Common Sense Initiative, agencies must balance the critical objectives of regulations that have an adverse impact on business with the costs of compliance by the regulated parties. Agencies should promote transparency, responsiveness,

predictability, and flexibility while developing regulations that are fair and easy to follow. Agencies should prioritize compliance over punishment, and to that end, should utilize plain language in the development of regulations.

Reason for Submission

1. **R.C. 106.03 and 106.031 require agencies, when reviewing a rule, to determine whether the rule has an adverse impact on businesses as defined by R.C. 107.52. If the agency determines that it does, it must complete a business impact analysis and submit the rule for CSI review.**

   Which adverse impact(s) to businesses has the agency determined the rule(s) create?

   The rule(s):

   a. ☐ **Requires a license, permit, or any other prior authorization to engage in or operate a line of business.**

   b. ☒ **Imposes a criminal penalty, a civil penalty, or another sanction, or creates a cause of action for failure to comply with its terms.**

   - Possession of a schedule I controlled substance imposes a criminal penalty.

   c. ☐ **Requires specific expenditures or the report of information as a condition of compliance.**

   d. ☐ **Is likely to directly reduce the revenue or increase the expenses of the lines of business to which it will apply or applies.**

Regulatory Intent

2. **Please briefly describe the draft regulation in plain language.**
   Please include the key provisions of the regulation as well as any proposed amendments.

Amend:

- 4729:9-1-01 - Updates the incorporation by reference to the temporary federal schedules. Adds the following compounds as schedule I controlled substances:
  - 2-Methyl-AP-237 (1-[2-methyl-4-[(E)-3-phenylprop-2-enyl]piperazin-1-yl]butan-1-one).
  - AP-237 (1-[4-(3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone).

3. **Please list the Ohio statute(s) that authorize the agency, board or commission to adopt the rule(s) and the statute(s) that amplify that authority.**

The proposed rule is authorized by sections 4729.26, 3719.44, 3719.41, and 3719.28 of the Ohio Revised Code.

4. **Does the regulation implement a federal requirement? Is the proposed regulation being adopted or amended to enable the state to obtain or maintain approval to administer and enforce a federal law or to participate in a federal program?**
   If yes, please briefly explain the source and substance of the federal requirement.

No.

5. **If the regulation includes provisions not specifically required by the federal government, please explain the rationale for exceeding the federal requirement.**

By scheduling 2-Methyl-AP-237 & AP-237 as schedule I controlled substances, the Board hopes to reduce access to the supply of these potentially lethal drugs and assist law enforcement is prosecuting individuals trafficking in these drugs. Further justification for scheduling these compounds can be found in the 8-factor analysis produced by the Board that is included as an appendix to this document.

6. **What is the public purpose for this regulation (i.e., why does the Agency feel that there needs to be any regulation in this area at all)?**

Section 4729.26 of the Ohio Revised Code authorizes the Board of Pharmacy to adopt rules governing the distribution of dangerous drugs.

Section 3719.28 of the Ohio Revised Code authorizes the Board of Pharmacy to adopt rules for the administration and enforcement of Chapter 3719. of the Revised Code in order to prescribe the manner of keeping and the form and content of records to be kept by persons authorized to manufacture, distribute, dispense, prescribe, or administer.

Section 3719.44 of the Ohio Revised Code authorizes the Board of Pharmacy to do any of the following with respect to schedules I, II, III, IV, and V established by rule adopted under section 3719.41 of the Revised Code:

(1) Add a previously unscheduled compound, mixture, preparation, or substance to any schedule;

(2) Transfer a compound, mixture, preparation, or substance from one schedule to another, provided the transfer does not have the effect under this chapter of providing less stringent control of the compound, mixture, preparation, or substance than is provided under the federal drug abuse control laws;

(3) Remove a compound, mixture, preparation, or substance from the schedules where the board had previously added the compound, mixture, preparation, or substance to the schedules, provided that the removal shall not have the effect under this chapter of providing less stringent control of the compound, mixture, preparation, or substance than is provided under the federal drug abuse control laws.

By scheduling 2-Methyl-AP-237 & AP-237 as schedule I controlled substances, the Board hopes to reduce access to the supply of these potentially lethal drugs and assist law enforcement is prosecuting individuals trafficking in these drugs. Further justification for scheduling these compounds can be found in the 8-factor analysis produced by the Board that is included as an appendix to this document.

7. How will the Agency measure the success of this regulation in terms of outputs and/or outcomes?

The success of the regulation will be measured by having the rule written in plain language, licensee compliance with the rules, and minimal questions from licensees regarding the provisions of the rules.

8. Are any of the proposed rules contained in this rule package being submitted pursuant to R.C. 101.352, 101.353, 106.032, 121.93, or 121.931?
If yes, please specify the rule number(s), the specific R.C. section requiring this submission, and a detailed explanation.

No.

Development of the Regulation

9. Please list the stakeholders included by the Agency in the development or initial review of the draft regulation.
If applicable, please include the date and medium by which the stakeholders were initially contacted.

This rule package was developed in consultation with the Ohio Department of Public Safety and the Emerging Drug Science Working Group (EDSWG). The EDSWG, convened by Ohio DPS, seeks to mitigate the challenges experienced with emerging drug data through regular communications with Ohio

forensic scientists in the fields of drug chemistry, toxicology as well as participation from public universities with forensic programs.

10. What input was provided by the stakeholders, and how did that input affect the draft regulation being proposed by the Agency?

The Ohio Department of Public Safety and its Emerging Drug Science Working Group provided all relevant data and source materials to develop the 8-factor analysis required to schedule 2-Methyl-AP-237 & AP-237.

11. What scientific data was used to develop the rule or the measurable outcomes of the rule? How does this data support the regulation being proposed?

Scientific data used to develop this rule is included as an appendix to this document. This data were used to develop the 8-fact analysis as required by 3719.44.

12. What alternative regulations (or specific provisions within the regulation) did the Agency consider, and why did it determine that these alternatives were not appropriate? If none, why didn't the Agency consider regulatory alternatives?

As the regulation is essential to protecting the public's safety by ensuring uniform rules for controlled substances, the State of Ohio Board of Pharmacy did not consider any regulatory alternatives.

13. Did the Agency specifically consider a performance-based regulation? Please explain. ***Performance-based regulations define the required outcome, but don't dictate the process the regulated stakeholders must use to achieve compliance.***

The Board did not consider a performance-based regulation for the rule in this package. It is the Board's responsibility to ensure that regulations are consistent throughout the state. It was the determination of the Board that the rule did not lend itself to performance-based regulations.

14. What measures did the Agency take to ensure that this regulation does not duplicate an existing Ohio regulation?

The Board of Pharmacy's Director of Policy and Communications reviewed the proposed rules to ensure that the regulations do not duplicate another State of Ohio Board of Pharmacy regulation.

15. Please describe the Agency's plan for implementation of the regulation, including any measures to ensure that the regulation is applied consistently and predictably for the regulated community.

The rule will be posted on the Board of Pharmacy's web site, information concerning the rule will be included in materials e-mailed to licensees, law enforcement, and laboratories. Board of Pharmacy staff are also available via phone or email to answer questions regarding implementation of the rule.

Board of Pharmacy staff receive regular updates on rules via a monthly internal newsletter, biannual staff meetings featuring a regulatory update, mandatory all-day law reviews for new employees, email updates and quarterly webinars from the Director of Policy and Communications and feedback from the Board's legal department for every citation submitted.

Adverse Impact to Business

16. Provide a summary of the estimated cost of compliance with the rule. Specifically, please do the following:

a. Identify the scope of the impacted business community; and

Persons possessing 2-Methyl-AP-237 & AP-237. NOTE: Research and other approved labs are lawfully able to possess schedule I controlled substances with valid licensure from the DEA and the Board of Pharmacy.

b. Identify the nature of all adverse impact (e.g., fees, fines, employer time for compliance,); and

Violation of these rules would result in a criminal penalty in accordance with Chapter 2925 of the Ohio Revised Code.

c. Quantify the expected adverse impact from the regulation.
The adverse impact can be quantified in terms of dollars, hours to comply, or other factors; and may be estimated for the entire regulated population or for a "representative business." Please include the source for your information/estimated impact.

The rule should not have any adverse impact on business, as it is intended to target a drug that has not been approved by the FDA and has no current medical use.

17. Why did the Agency determine that the regulatory intent justifies the adverse impact to the regulated business community?

After a thorough review of all available data, the State of Ohio Board of Pharmacy determined that each AP-237 and 2-methyl-AP-237:

1. Has a high potential for abuse;
2. Has no accepted medical use in treatment in this state;
3. Lacks accepted safety for use in treatment under medical supervision;
4. Follows the same history and pattern of abuse as other schedule I mu-opioid receptor agonists;
5. Poses a risk to the public health of the citizens in this state; and
6. Has an associated physiological dependence liability.

Regulatory Flexibility

18. Does the regulation provide any exemptions or alternative means of compliance for small businesses? Please explain.

This rule package does not provide any exemptions or alternative means of compliance for small businesses. The law does not differentiate on the size of the business and therefore the regulation is uniform across Ohio.

19. How will the agency apply Ohio Revised Code section 119.14 (waiver of fines and penalties for paperwork violations and first-time offenders) into implementation of the regulation?

The State of Ohio Board of Pharmacy does not fine licensees or impose penalties for first-time paperwork violations. However, any failure of a standard of care in the distribution of dangerous drugs is not considered a paperwork error but a quality assurance issue by the licensee that is necessary for the protection of the public.

20. What resources are available to assist small businesses with compliance of the regulation?

Board of Pharmacy staff is available by telephone and e-mail to answer questions. Board staff members also provide presentations to groups and associations who seek updates on current regulations. Additionally, staff are trained to educate licensees on compliance with all Board of Pharmacy rules and regulations.

Rule 4729:9-1-01 | Schedule I controlled substances. (AMEND)

Pursuant to section 3719.41 of the Revised Code, controlled substance schedule I is hereby established, which schedules include the following, subject to amendment pursuant to section 3719.43 or 3719.44 of the Revised Code.

(A) As used in this rule:

(1) "Synthetic" unless specifically excepted or unless listed in another schedule, means any substance, material, compound, mixture, or preparation that contains any quantity of a substance made artificially by chemical reaction.

(2) "Pharmacophore" means the portion of a chemical structure that confers the activity of the substance.

(3) "A report from an established forensic laboratory" means a laboratory report from the bureau of criminal identification and investigation, or a laboratory operated by another law enforcement agency, or a laboratory established by or under the authority of an institution of higher education that has its main campus in this state and that is accredited by the association of American universities or the north central association of colleges and secondary schools, primarily for the purpose of providing scientific services to law enforcement agencies and signed by the person performing the analysis as defined in division (A) of section 2925.51 of the Revised Code.

(4) "Synthetic cannabinoids" are drugs commonly found in herbal incense products (common names include but are not limited to: spice, blaze, devil's advocate, genie, smoke, sense, zohai, spike 99, and K2) that may mimic the effects of delta-9-tetrahydrocannabinol (THC), an active central nervous system constituent compound of marijuana.

(B) Narcotics-opiates

Any of the following opiates, including their isomers, esters, ethers, salts, and salts of isomers, esters, and ethers, unless specifically excepted under federal drug abuse control laws, whenever the existence of these isomers, esters, ethers, and salts is possible within the specific chemical designation (for purposes of 3-methylthiofentanyl only, the term isomer includes the optical and geometric isomers):

(1) Acetyl-alpha-methylfentanyl (N-[1-(1-methyl-2-phenethyl)-4-piperidinyl]-N-phenylacetamide);

(2) Acetylmethadol;

(3) Acetyl fentanyl (N-(1-phenethylpiperidin-4-yl)-N-phenylacetamide);

(4) Acryl fentanyl (N-(1-phenethylpiperidin-4-yl)-N-phenylacrylamide; other name: acryloylfentanyl);

(5) AH-7921 (3,4-dichloro-N-[(1-dimethylamino) cyclohexylmethyl]benzamide;

(6) Allylprodine;

(7) Alphacetylmethadol (except levo-alphacetylmethadol, also known as levo-alpha- acetylmethadol, levomethadyl acetate, or LAAM);

(8) Alphameprodine;

(9) Alphamethadol;

(10) Alpha-methylfentanyl (N-[1-(alpha-methyl-beta-phenyl)ethyl-4-piperidyl] propionanilide; 1- (1-methyl-2-phenylethyl)-4-(N-propanilido) piperidine);

(11) Alpha-methylthiofentanyl (N-[1-methyl-2-(2-thienyl)ethyl-4-piperidinyl]-N- phenylpropanamide);

(12) Benzethidine;

(13) Betacetylmethadol;

(14) Beta-hydroxyfentanyl (N-[1-(2-hydroxy-2-phenethyl-4-piperidinyl]-N- phenylpropanamide);

(15) Beta-hydroxy-3-methylfentanyl (other name: N-[1-(2-hydroxy-2-phenethyl)-3-methyl-4- piperidinyl]-N- phenylpropanamide);

(16) N-[1-[2-hydroxy-2-(thiophen-2-yl)ethyl]piperidin-4-yl]-N-phenylpropionamide (other name: beta-Hydroxythiofentanyl);

(17) Betameprodine;

(18) Betamethadol;

(19) Betaprodine;

(20) Butyryl fentanyl (N-(1-phenethylpiperidin-4-yl)-N-phenylbutyramide);

(21) Clonitazene;

(22) Dextromoramide;

(23) Diampromide;

(24) Diethylthiambutene;

(25) Difenoxin;

(26) Dimenoxadol;

(27) Dimepheptanol;

(28) Dimethylthiambutene;

(29) Dioxaphetyl butyrate;

(30) Dipipanone;

(31) Ethylmethylthiambutene;

(32) Etonitazene;

(33) Etoxeridine;

(34) 4-Fluoroisobutyryl fentanyl (N-(4-fluorophenyl)-N-(1-phenethylpiperidin-4-yl)isobutyramide; other name: para-fluoroisobutyryl fentanyl);

(35) Furanyl fentanyl (N-(1-phenethylpiperidin-4-yl)-N-phenylfuran-2-carboxamide);

(36) Furethidine;

(37) Hydroxypethidine;

(38) Ketobemidone;

(39) Levomoramide;

(40) Levophenacylmorphan;

(41) 3-methylfentanyl (N-[3-methyl-1-(2-phenylethyl)-4-piperidyl]-N- phenylpropanamide);

(42) 3-methylthiofentanyl (N-[3-methyl-1-[2-(thienyl)ethyl]-4-piperidinyl]-N- phenylpropanamide);

(43) Morpheridine;

(44) MPPP (1-methyl-4-phenyl-4-propionoxypiperidine);

(45) MT-45 (1-cyclohexyl-4-(1,2-diphenylethyl)piperazine);

(46) Noracymethadol;

(47) Norlevorphanol;

(48) Normethadone;

(49) Norpipanone;

(50) Ocfentanil (N-(2-fluorophenyl)-2-methoxy-N-(1-phenethylpiperidin-4-yl)acetamide);

(51) Para-fluorofentanyl (N-(4-fluorophenyl)-N-[1-(2-phenethyl)-4-piperidinyl]propanamide;

(52) PEPAP (1-(2-phenethyl)-4-phenyl-4-acetoxypiperidine;

(53) Phenadoxone;

(54) Phenampromide;

(55) Phenomorphan;

(56) Phenoperidine;

(57) Piritramide;

(58) Proheptazine;

(59) Properidine;

(60) Propiram;

(61) Racemoramide;

(62) Tetrahydrofuranyl fentanyl (N-(1-phenethylpiperidin-4-yl)-N-phenyltetrahydrofuran-2-carboxamide);

(63) Thiofentanyl (N-phenyl-N-[1-(2-thienyl)ethyl-4-piperidinyl]-propanamide;

(64) Tilidine;

(65) Trimeperidine;

(66) U-47700 (3,4-Dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methylbenzamide);

(67) Except as otherwise provided in this chapter, any compound that meets all of the following fentanyl pharmacophore requirements to bind at the mu receptor, as identified by a report from an established forensic laboratory:

(a) A chemical scaffold consisting of both of the following:

(i) A five, six, or seven member ring structure containing a nitrogen, whether or not further substituted;

(ii) An attached nitrogen to the ring, whether or not that nitrogen is enclosed in a ring structure, including an attached aromatic ring or other lipophilic group to that nitrogen.

(b) A polar functional group attached to the chemical scaffold, including but not limited to, a hydroxyl, ketone, amide, or ester;

(c) An alkyl or aryl substitution off the ring nitrogen of the chemical scaffold; and

(d) The compound has not been approved for medical use by the United States food and drug administration.

(68) N,N-Diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine (isotonitazene).

(69) 2-Methyl-AP-237 (1-[2-methyl-4-[(E)-3-phenylprop-2-enyl]piperazin-1-yl]butan-1-one).

(70) AP-237 (1-[4-(3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone).

(C) Narcotics-opium derivatives

Any of the following opium derivatives, including their salts, isomers, and salts of isomers, unless specifically excepted under federal drug abuse control laws, whenever the existence of these salts, isomers, and salts of isomers is possible within the specific chemical designation:

(1) Acetorphine;

(2) Acetyldihydrocodeine;

(3) Benzylmorphine;

(4) Codeine methylbromide;

(5) Codeine-n-oxide;

(6) Cyprenorphine;

(7) Desomorphine;

(8) Dihydromorphine;

(9) Drotebanol;

(10) Etorphine (except hydrochloride salt);

(11) Heroin;

(12) Hydromorphinol;

(13) Methyldesorphine;

(14) Methyldihydromorphine;

(15) Morphine methylbromide;

(16) Morphine methylsulfonate;

(17) Morphine-n-oxide;

(18) Myrophine;

(19) Nicocodeine;

(20) Nicomorphine;

(21) Normorphine;

(22) Pholcodine;

(23) Thebacon;

(24) 6-monoacetylmorphine (6-MAM).

(D) Hallucinogens

Any material, compound, mixture, or preparation that contains any quantity of the following hallucinogenic substances, including their salts, isomers, and salts of isomers, unless specifically excepted under federal drug abuse control laws, whenever the existence of these salts, isomers, and salts of isomers is possible within the specific chemical designation. For the purposes of this division only, "isomer" includes the optical isomers, position isomers, and geometric isomers.

(1) Alpha-ethyltryptamine (some trade or other names: etryptamine; Monase; alpha-ethyl-1H- indole-3-ethanamine; 3-(2-aminobutyl) indole; alpha-ET; and AET);

(2) 4-bromo-2,5-dimethoxyamphetamine (some trade or other names: 4-bromo-2,5-dimethoxy- alpha-methyphenethylamine; 4-bromo-2,5-DMA);

(3) 4-bromo-2,5-dimethoxyphenethylamine (some trade or other names: 2-(4-bromo-2,5-dimethoxyphenyl)-1-aminoethane; alpha-desmethyl DOB; 2C-B, Nexus);

(4) 2,5-dimethoxyamphetamine (some trade or other names: 2,5-dimethoxy-alpha- methylphenethylamine; 2,5-DMA);

(5) 2,5-dimethoxy-4-ethylamphetamine (some trade or other names: DOET);

(6) 2,5-dimethoxy-4-(n)-propylthiophenethylamine (other name: 2C-T-7);

(7) 4-methoxyamphetamine (some trade or other names: 4-methoxy-alpha- methylphenethylamine; paramethoxyamphetamine; PMA);

(8) 5-methoxy-3,4-methylenedioxy-amphetamine;

(9) 4-methyl-2,5-dimethoxy-amphetamine (some trade or other names: 4-methyl-2,5-dimethoxy- alpha-methylphenethylamine; "DOM" and "STP");

(10) 3,4-methylenedioxy amphetamine (MDA);

(11) 3,4-methylenedioxymethamphetamine (MDMA);

(12) 3,4-methylenedioxy-N-ethylamphetamine (also known as N-ethyl-alpha-methyl-3,4(methylenedioxy)phenethylamine, N-ethyl MDA, MDE, MDEA);

(13) N-hydroxy-3,4-methylenedioxyamphetamine (also known as N-hydroxy-alpha-methyl-3,4(methylenedioxy)phenethylamine and N-hydroxy MDA);

(14) 3,4,5-trimethoxy amphetamine;

(15) 5-methoxy-N,N-dimethyltryptamine (some trade or other names: 5-methoxy-3-[2-(dimethylamino)ethyl]indole; 5-MeO-DMT);

(16) Alpha-methyltryptamine (other name: AMT);

(17) Bufotenine (some trade or other names: 3-(beta-dimethylaminoethyl)-5-hydroxyindole; 3-(2-dimethylaminoethyl)-5-indolol; N, N-dimethylserotonin; 5-hydroxy-N, N-dimethyltryptamine; mappine);

(18) Diethyltryptamine (some trade or other names: N, N-diethyltryptamine; DET);

(19) Dimethyltryptamine (some trade or other names: DMT);

(20) 5-methoxy-N,N-diisopropyltryptamine (other name: 5-MeO-DIPT);

(21) Ibogaine (some trade or other names: 7-ethyl-6,6beta,7,8,9,10,12,13-octahydro-2-methoxy- 6,9-methano- 5H-pyrido[1',2':1,2] azepino [5, 4-b] indole; tabernanthe iboga);

(22) Lysergic acid diethylamide;

(23) Marihuana;

(24) Mescaline;

(25) Parahexyl (some trade or other names: 3-hexyl-1- hydroxy-7,8,9,10-tetrahydro-6,6,9- trimethyl-6H-dibenzo[b,d]pyran; synhexyl);

(26) Peyote (meaning all parts of the plant presently classified botanically as "Lophophora williamsii Lemaire," whether growing or not, the seeds of that plant, any extract from any part of that plant, and every compound, manufacture, salts, derivative, mixture, or preparation of that plant, its seeds, or its extracts);

(27) N-ethyl-3-piperidyl benzilate;

(28) N-methyl-3-piperidyl benzilate;

(29) Psilocybin;

(30) Psilocyn;

(31) Tetrahydrocannabinols (synthetic equivalents of the substances contained in the plant, or in the resinous extractives of Cannabis, sp. and/or synthetic substances, derivatives, and their isomers with similar chemical structure and pharmacological activity such as the following: delta-1- cis or trans tetrahydrocannabinol, and their optical isomers; delta-6-cis or trans tetrahydrocannabinol, and their optical isomers; delta-3,4-cis or trans tetrahydrocannabinol, and its optical isomers. (Since nomenclature of these substances is not internationally standardized, compounds of these structures, regardless of numerical designation of atomic positions, are covered.)), excluding any of the following:

(a) Tetrahydrocannabinols found in "hemp" and "hemp products" as those terms are defined in section 928.01 of the Revised Code; and

(b) Any other substance containing tetrahydrocannabinols as authorized in this chapter of the Administrative Code.

(32) N-ethyl-1- phenylcyclohexylamine (1-phenylcyclohexyl)ethylamine; N-(1-phenylcyclohexyl)ethylamine; cyclohexamine; PCE);

(33) 1-(1- phenylcyclohexyl)pyrrolidine (PCPy; PHP);

(34) 1-[1-(2-thienyl)-cyclohexyl]- piperidine (2-thienyl analog of phencyclidine; TPCP; TCP);

(35) 1-[1-(2-thienyl)cyclohexyl]pyrrolidine (some other names: TCPy);

(36) 4-methylmethcathinone (mephedrone);

(37) 3,4-methylenedioxypyrovalerone (MDPV);

(38) 3,4-Methylenedioxy-N-methylcathinone (Methylone);

(39) Hashish;

(40) Salvia divinorum;

(41) Salvinorin A;

(42) (1-pentylindol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methanone (UR-144);

(43) 1-pentyl-3-(1-adamantoyl)indole (AB-001);

(44) N-adamantyl-1-pentylindole-3-carboxamide (APICA, 2NE1);

(45) N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide (AB-FUBINACA);

(46) N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide (ADB-PINACA);

(47) N-adamantyl-1-pentylindazole-3-carboxamide (APINACA, AKB48);

(48) 2-ethylamino-2-(3-methoxyphenyl)cyclohexanone (methoxetamine);

(49) N,N-diallyl-5-methoxytryptamine (5MeO-DALT);

(50) [1-(5-fluoropentylindol-3-yl)]-(2,2,3,3-tetramethylcyclopropyl)methanone (5-fluoropentyl-UR-144; XLR11);

(51) [1-(5-chloropentylindol-3-yl)]-(2,2,3,3-tetramethylcyclopropyl)methanone (5-chloropentyl-UR-144);

(52) [1-(5-bromopentylindol-3-yl)]-(2,2,3,3-tetramethylcyclopropyl)methanone (5-bromopentyl-UR-144);

(53) {1-[2-(4-morpholinyl)ethyl]indol-3-yl}-(2,2,3,3-tetramethylcyclopropyl) methanone (A- 796,260);

(54) 1-[(N-methylpiperidin-2-yl)methyl]-3-(1-adamantoyl)indole (AM1248);

(55) N-adamantyl-1-(5-fluoropentylindole)-3-carboxamide (5F-APICA, STS135);

(56) 5-(2-aminopropyl)benzofuran (5-APB);

(57) 6-(2-aminopropyl)benzofuran (6-APB);

(58) 5-(2-aminopropyl)-2,3-dihydrobenzofuran (5-APDB);

(59) 6-(2-aminopropyl)-2,3-dihydrobenzofuran (6-APDB);

(60) Benzothiophenylcyclohexylpiperidine (BTCP);

(61) 2-(2,5-Dimethoxy-4-ethylphenyl)ethanamine (2C-E);

(62) 2-(2,5-Dimethoxy-4-methylphenyl)ethanamine (2C-D);

(63) 2-(4-Chloro-2,5-dimethoxyphenyl)ethanamine (2C-C);

(64) 2-(4-Iodo-2,5-dimethoxyphenyl)ethanamine (2C-I);

(65) 2-[4-(Ethylthio)-2,5-dimethoxyphenyl]ethanamine (2C-T-2);

(66) 2-[4-(Isopropylthio)-2,5-dimethoxyphenyl]ethanamine (2C-T-4);

(67) 2-(2,5-Dimethoxyphenyl)ethanamine (2C-H);

(68) 2-(2,5-Dimethoxy-4-nitro-phenyl)ethanamine (2C-N);

(69) 2-(2,5-Dimethoxy-4-(n)-propylphenyl)ethanamine (2C-P);

(70) 4-methoxymethamphetamine (PMMA);

(71) 5,6 - Methylenedioxy-2-aminoindane (MDAI);

(72) 5-iodo-2-aminoindiane (5-IAI);

(73) 2-(4-iodo-2,5-dimethoxyphenyl)-N- [(2-methoxyphenyl)methyl]ethanamine(25I-NBOMe);

(74) 2-(4-chloro-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine (25C-NBOMe, 2C-C- NBOMe);

(75) 2-(4-bromo-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)ethanamine (25B-NBOMe, 2C-B- NBOMe);

(76) 4-methyl-N-ethylcathinone (4-MEC);

(77) 4-methyl-alpha-pyrrolidinopropiophenone (4-MePPP);

(78) Alpha-pyrrolidinopentiophenone (alpha-PVP);

(79) 1-(1,3-benzodioxol-5-yl)-2-(methylamino)butan-1-one (butylone, bk-MBDB);

(80) 2-(methylamino)-1-phenylpentan-1-one (pentedrone);

(81) 1-(1,3-benzodioxol-5-yl)-2-(methylamino)pentan-1- one (pentylone, bk-MBDP);

(82) 4-fluoro-N-methylcathinone (4-FMC; flephedrone);

(83) 3-fluoro-N-methylcathinone (3-FMC);

(84) 1-(naphthalen-2-yl)-2-(pyrrolidin-1-yl)pentan-1-one (naphyrone);

(85) Alpha-pyrrolidinobutiophenone (alpha-PBP);

(86) N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide (AB-CHMINACA);

(87) N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide (AB-PINACA);

(88) [1-(5-fluoropentyl)-1H-indazol-3-yl](naphthalen-1-yl)methanone (THJ-2201);

(89) N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide, its optical, positional, and geometric isomers, salts and salts of isomers (Other names: MAB- CHMINACA; ADB-CHMINACA);

(90) Diphenylprolinol (diphenyl(pyrrolidin-2-yl)methanol, D2PM);

(91) Desoxypipradrol (2-benzhydrylpiperidine);

(92) Synthetic cannabinoids - unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation that contains any quantity of a synthetic cannabinoid found to be in any of the following chemical groups or any of those groups which contain any synthetic cannabinoid salts, isomers, or salts of isomers, whenever the existence of such salts, isomers, or salts of isomers is possible within the specific chemical groups:

(a) Naphthoylindoles: any compound containing a 3-(1-naphthoyl)indole structure with or without substitution at the nitrogen atom of the indole ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl,

cycloalkylethyl, (N-methylpiperidin-2-yl)methyl, cyanoalkyl, (N-methylpyrrolidin-2-yl)methyl, (tetrahydropyran-4-yl)methyl, ((N-methyl)-3-morpholinyl)methyl, or 2-(4-morpholinyl)ethyl group, whether or not further substituted on the indole ring to any extent or whether or not substituted on the naphthyl group to any extent. Naphthoylindoles include, but are not limited to, 1-[2-(4-morpholinyl)ethyl]-3-(1-naphthoyl)indole (JWH-200); 1-(5-fluoropentyl)-3-(1-naphthoyl)indole (AM2201), 1-pentyl-3-(1-naphthoyl)indole (JWH-018), and 1-butyl-3-(1-naphthoyl)indole (JWH- 073).

(b) Naphthylmethylindoles: any compound containing a 1H-indol-3-yl-(1-naphthyl)methane structure with or without substitution at the nitrogen atom of the indole ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl, cyanoalkyl, (N- methylpyrrolidin-2-yl)methyl, (tetrahydropyran-4-yl)methyl, ((N-methyl)-3-morpholinyl)methyl, or 2-(4-morpholinyl)ethyl group, whether or not further substituted on the indole ring to any extent or whether or not substituted on the naphthyl group to any extent. Naphthylmethylindoles include, but are not limited to, (1-pentylindol-3-yl)(1-naphthyl)methane (JWH-175).

(c) Naphthoylpyrroles: any compound containing a 3-(1-naphthoyl)pyrrole structure with or without substitution at the nitrogen atom of the pyrrole ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl, cyanoalkyl, (N-methylpyrrolidin- 2-yl)methyl, (tetrahydropyran-4-yl)methyl, ((N-methyl)-3-morpholinyl)methyl, or 2-(4- morpholinyl)ethyl group, whether or not further substituted on the pyrrole ring to any extent or whether or not substituted on the naphthyl group to any extent. Naphthoylpyrroles include, but are not limited to, 1-hexyl-2-phenyl-4-(1-naphthoyl)pyrrole (JWH-147).

(d) Naphthylmethylindenes: any compound containing a naphthylmethylideneindene structure with or without substitution at the 3-position of the indene ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl, cyanoalkyl, (N-methylpyrrolidin- 2-yl)methyl, (tetrahydropyran-4-yl)methyl, ((N-methyl)-3-morpholinyl)methyl, or 2-(4- morpholinyl)ethyl group, whether or not further substituted on the indene group to any extent or whether or not substituted on the naphthyl group to any extent. Naphthylmethylindenes include, but are not limited to, (1-[(3-pentyl)-1H-inden-1-ylidene)methyl]naphthalene (JWH-176).

(e) Phenylacetylindoles: any compound containing a 3-phenylacetylindole structure with or without substitution at the nitrogen atom of the indole ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl, cyanoalkyl, (N-methylpyrrolidin-2-yl)methyl, (tetrahydropyran-4-yl)methyl, ((N-methyl)-3-morpholinyl)methyl, or 2-(4-morpholinyl)ethyl group, whether or not further substituted on the indole ring to any extent or whether or not substituted on the phenyl group to any extent. Phenylacetylindoles include, but are not limited to, 1-pentyl-3-(2-

methoxyphenylacetyl)indole (JWH-250), and 1-(2-cyclohexylethyl)-3-(2- methoxyphenylacetyl)indole (RCS-8); 1-pentyl-3-(2-chlorophenylacetyl)indole (JWH-203).

(f) Cyclohexylphenols: any compound containing a 2-(3-hydroxycyclohexyl)phenol structure with or without substitution at the 5-position of the phenolic ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl, cyanoalkyl, (N-methylpyrrolidin- 2-yl)methyl, (tetrahydropyran-4-yl)methyl, ((N-methyl)-3-morpholinyl)methyl, or 2-(4- morpholinyl)ethyl group, whether or not further substituted on the cyclohexyl group to any extent. Cyclohexylphenols include, but are not limited to, 5-(1,1-dimethylheptyl)-2-[(1R,3S)-3- hydroxycyclohexyl]-phenol (some trade or other names: CP-47,497) and 5-(1,1-dimethyloctyl)-2- [(1R,3S)-3-hydroxycyclohexyl]-phenol (some trade or other names: cannabicyclohexanol; CP- 47,497 C8 homologue).

(g) Benzoylindoles: any compound containing a 3-(1-benzoyl)indole structure with or without substitution at the nitrogen atom of the indole ring by an alkyl, haloalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, (N-methylpiperidin-2-yl)methyl, cyanoalkyl, (N-methylpyrrolidin-2-yl)methyl, (tetrahydropyran-4-yl)methyl, ((N-methyl)-3-morpholinyl)methyl or 2-(4-morpholinyl)ethyl group, whether or not further substituted on the indole ring to any extent or whether or not substituted on the phenyl group to any extent. Benzoylindoles include, but are not limited to, 1-pentyl-3-(4- methoxybenzoyl)indole (RCS-4), 1-[2-(4-morpholinyl)ethyl]-2-methyl-3-(4-methoxybenzoyl)indole (Pravadoline or WIN 48, 098).

(93) Quinolin-8-yl 1-pentyl-1H-indole-3-carboxylate (PB-22; QUPIC);

(94) Quinolin-8-yl 1-(5-fluoropentyl)-1H-indole-3-carboxylate (5-fluoro-PB-22; 5F-PB-22);

(95) Except as otherwise provided in this rule, any compound that meets at least three of the following cannabinoid pharmacophore requirements to bind at the CB1 and CB2 receptors, as identified by a report from an established forensic laboratory:

(a) A chemical scaffold consisting of substituted or non-substituted ring structures that facilitate binding of required elements (such as: indole compounds, indazoles, benzimidazoles or other ring types);

(b) Alkyl or aryl side chain off the chemical scaffold providing hydrophobic interaction with the CB1 and CB2 receptors;

(c) Carbonyl or ester or equivalent for hydrogen bonding;

(d) Cyclohexane, naphthalene ring, substituted butanamide or equivalent for steric requirements for CB1 and CB2 receptor binding.

(E) Depressants

Any material, compound, mixture, or preparation that contains any quantity of the following substances having a depressant effect on the central nervous system, including their salts, isomers, and salts of isomers, unless specifically excepted under federal drug abuse control laws, whenever the existence of these salts, isomers, and salts of isomers is possible within the specific chemical designation:

(1) Mecloqualone;

(2) Methaqualone;

(3) Except as listed in rule 4729:9-1-03 of the Administrative Code, gamma-hydroxybutyric acid (some other names include GHB; gamma-hydroxybutyrate; 4-hydroxybutyrate; 4-hydroxybutanoic acid; sodium oxybate; sodium oxybutyrate);

(4) Etizolam (4-(2-chlorophenyl)-2-ethyl-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3- a][1,4]diazepine);

(5) Except as otherwise provided in this chapter, any compound that contains the following structural requirements of a benzodiazepine pharmacophore, as identified by a report from an established forensic laboratory:

A core structure consisting of a benzene ring fused to the seven-membered diazepine ring with a 5-aryl substituent aka 5-aryl-1,4-benzodiazepine for binding to the GABA receptor. Regardless of impact on the lipophilic properties of the compound, a benzodiazepine pharmacophore may contain a variety of functional groups including, but not limited to, aldehydes, ketones, esters, and amides.

This paragraph only applies to a compound that has not been approved for medical use by the United States food and drug administration.

(F) Stimulants

Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation that contains any quantity of the following substances having a stimulant effect on the central nervous system, including their salts, isomers, and salts of isomers:

(1) Aminorex (some other names: aminoxaphen; 2-amino-5-phenyl-2-oxazoline; or 4,5-dihydro-5- phenyl-2-oxazolamine);

(2) N-Benzylpiperazine (some other names: BZP, 1-benzylpiperazine);

(3) Cathinone (some trade or other names: 2-amino-1-phenyl-1-propanone, alpha- aminopropiophenone, 2-aminopropiophenone, and norephedrone);

(4) Fenethylline;

(5) Methcathinone (some other names: 2-(methylamino)-propiophenone; alpha-(methylamino)propiophenone; 2-(methylamino)-1-phenylpropan-1-one; alpha-N-methylaminopropiophenone; monomethylpropion; ephedrone; N-methylcathinone; methylcathinone; AL-464; AL-422; AL-463 and UR1432), its salts, optical isomers and salts of optical isomers;

(6) (+/-)cis-4-methylaminorex ((+/-)cis-4,5-dihydro-4-methyl-5-phenyl-2-oxazolamine);

(7) N-ethylamphetamine;

(8) N,N-dimethylamphetamine (also known as N,N-alpha-trimethyl-benzeneethanamine; N,N- alpha-trimethylphenethylamine);

(9) N-methyl-1-(thiophen-2-yl) propan-2-amine (methio-propamine);

(10) Substituted cathinones - any compound except bupropion or compounds listed under a different schedule, structurally derived from 2-aminopropan-1-one by substitution at the 1-position with either phenyl, naphthyl, or thiophene ring systems, whether or not the compound is further modified in any of the following ways:

(a) By substitution in the ring system to any extent with alkyl, alkylenedioxy, alkoxy, haloalkyl, hydroxyl, or halide substituents, whether or not further substituted in the ring system by one or more other univalent substituents;

(b) By substitution at the 3-position with an acyclic alkyl substituent;

(c) By substitution at the 2-amino nitrogen atom with alkyl, dialkyl, benzyl, or methoxybenzyl groups;

(d) By inclusion of the 2-amino nitrogen atom in a cyclic structure.

(11) Except as otherwise provided in this rule, any compound that contains the structural requirements of the cathinone pharmacophore, as identified by a report from an established forensic laboratory.

(G) For the purpose of complying with federal rule, all materials, compounds, mixtures or preparations which contain any substance temporarily placed in schedule I pursuant to 21 U.S.C. 811 by the United States drug enforcement administration (~~11/5/2020~~ 1/11/2022).

Appendix I - 8-Factor Analysis

A RESOLUTION: PROPOSED SCHEDULING ACTION

Adopted 1/10/22

Section 1: Summary

The State of Ohio Board of Pharmacy (BOP), pursuant to section 3719.44 of the Ohio Revised Code, proposes the placement of the following into Schedule I:

*2-Methyl-AP-237 (*1-[2-methyl-4-[(*E*)-3-phenylprop-2-enyl]piperazin-1-yl]butan-1-one*), as a narcotic-opiate.*

AP-237 (1-[4-(3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone), as a narcotic-opiate.

Section 2: Background

Pursuant to section 3719.44 the Board may add or transfer a compound, mixture, preparation, or substance to schedule I when it appears that there is a high potential for abuse, that it has no accepted medical use in treatment in this state, or that it lacks accepted safety for use in treatment under medical supervision.

In making a determination to add an unscheduled compound, the Board is required to consider the following 8 criteria:

(1) The actual or relative potential for abuse;
(2) The scientific evidence of the pharmacological effect of the substance;
(3) The state of current scientific knowledge regarding the substance;
(4) The history and current pattern of abuse;
(5) The scope, duration, and significance of abuse;
(6) The risk to the public health;
(7) The potential of the substance to produce psychic or physiological dependence liability; and
(8) Whether the substance is an immediate precursor.

Section 3: Evaluating 2-Methyl-AP-237 Under the Eight Criteria

(1) The actual or relative potential for abuse.

Appendix I - 8-Factor Analysis

The growing availability and abuse of novel psychoactive substances[1] (NPSs) over the past decade is unparalleled. A subset of NPSs are new synthetic opioids (NSOs). Attributed by some to a 2018 control measures in China aimed at reducing the availability of fentanyl-related compounds, non-fentanyl NSOs, such as AP-237 and 2-methyl-AP, have started to emerge on the illicit market. According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDD), 2019 brought eight NSOs that were not previously seen in forensic cases. Six of those NSOs were non-fentanyl opioids, including AP-237 and 2-methyl-AP-237. By the third quarter of 2021, 2-methyl-AP-237 was the second most frequently identified NSO in toxicology samples within the United States.[2]

Many of the NSOs illicitly available today were synthesized by pharmaceutical companies in the second half of the twentieth century. These syntheses were designed in an effort to identify compounds that are safer and more effective alternatives to morphine. Published literature related to these efforts—including patents—serve as a database for underground chemists to manufacture gray market NSOs.

2-methyl-AP-237 has a pharmacological profile similar to the mu-opioid agonist-like activity of a classical opioid. It is a methyl derivative of bucinnazine (AP-237), a therapeutic drug used to treat cancer pain in China. However, 2-methyl-AP-237 has no known approval for medical use, while AP-237 has no known medical use in the United States. Both are sold in the United States as designer drugs and research chemicals.

Nationally, actual abuse of 2-methyl-AP-237 has been reported in California, Florida, Iowa, Ohio, Pennsylvania, South Carolina, and Tennessee. Responses from Ohio crime labs queried while preparing this report illustrate that current 2-methyl-AP-237 abuse is seen in the northern portion of the state. AP-237 was present in at least one evidentiary item in Ohio. Like other non-controlled substances, however, quantifying actual abuse is elusive. Laboratories either do not target their analysis for the identification of the non-controlled substance or the reported findings are, "no controlled substance found."

Drug Fact Sheet: 2-Methyl-AP-237. Drug Enforcement Administration. (available at https://www.deadiversion.usdoj.gov/drug_chem_info/2-Methyl-AP-237.pdf) (last visited Dec. 20, 2021).

U.S. Drug Enforcement Administration, Diversion Control Division. (2021). *DEA-TOX: Alert Regarding 2-Methyl AP-237 – June 11, 2021.* Springfield, VA: U.S. Drug Enforcement Administration. (available at https://www.deadiversion.usdoj.gov/dea_tox/index.html) (last visited Dec. 20, 2021).

Vandeputte MM, Cannaert A, Stove CP. In vitro functional characterization of a panel of non-fentanyl opioid new psychoactive substances. Arch Toxicol. 94(11):3819-3830. (2020).

[1] NPSs are defined by the United Nations Office on Drugs and Crime (UNODC) as, "substance of abuse, either in pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat."

[2] According to the CFSRE, 2-methyl-AP-237 was identified second only to fluorofentanyl.

Lamy FR, Daniulaityte R, Barratt MJ, Lokala U, Sheth A, Carlson RG. Listed for sale: Analyzing data on fenanty, fentanyl analogs and other novel synthetic opioids on one cryptomarket. Drug and Alcohol Dependence. 213 (2020) 108115.

Center for Forensic Science Research and Education. 2021 Q3 NPS Opioids Trend Report (available at https://www.npsdiscovery.org/reports/trend-reports/) (last visited Dec. 27, 2021).

(2) The scientific evidence of the pharmacological effect of the substance.

Irikura and others (1968) illustrate that compounds substituted with a cinnamyl group at the N4 of the piperazine ring in 1-acyl-4-substituted piperazines show potent analgesic activity.

AP-237 is highly lipid soluble. This allows for efficient diffusion through membranes such as the blood brain barrier and direct binding to opioid receptors in the brain. AP-237 is one of the most potent of NSO piperazines.

Based on binding affinity, Vandeputte and others (2020) report that 2-methyl-AP-237 is 68–156 times less potent than fentanyl—fentanyl is approximate 100 more potent than morphine. Both Vandeputte and Volpe caution against using binding affinity exclusively to compare potency. Notably, as of June 2021, 2-methyl-AP-237 has been linked to at least two fatal overdose deaths in the United States.[3]

Resnik K, Brandao P, Amorim Alves E. DARK classics in chemical neuroscience: Bucinnazine. ACS Chem. Neurosci. 2021, 12, 3527–3534.

Drug Fact Sheet: 2-Methyl-AP-237. Drug Enforcement Administration. (available at https://www.deadiversion.usdoj.gov/drug_chem_info/2-Methyl-AP-237.pdf) (last visited Dec. 20, 2021).

Vandeputte MM, Cannaert A, Stove CP. In vitro functional characterization of a panel of non-fentanyl opioid new psychoactive substances. Arch Toxicol. 94(11):3819-3830. (2020).

Volpe DA, McMahon Tobin GA, Mellon RD, Kadki AG, Parker RJ, Colatsky T, Kropp TJ, Verbois SL (2011). Uniform assessment and ranking of opioid Mu receptor binding constants for selected opioid drugs. Reg. Tox. and Pharm. 59(2011) 385–390.

Irikura T, Masuzawa K, Nishino K, Kitagawa M, Uchida H, Ichinoseki N, Ito M. New Analgetic Agents. V. 1-Butyryl-4-Cinnamylpiperazine Hydrochloride and Related Compounds. J. Med. Chem. 1968, 11 (4), 801−804.

[3] These numbers are likely under reported as 2-methyl-AP-237, like other substances that are not explicitly controlled, is not reported or even targeted for analysis by most forensic laboratories.

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(3) The state of current scientific knowledge regarding the substance.

AP-237 and 2-methyl-AP-237[4] belong to a class of NSOs referred to as piperazines. Recent illicit drug patterns illustrate a trend toward the abuse of non-fentanyl related opioids. Despite clinical availability of AP-237 (bucinnazine) in China, even information related to its effects are limited. Less is known about AP-237's methylated derivative as it is not available for clinical purposes at all.

As discussed above, based on binding affinity, Vandeputte and others (2020) report that 2-methyl-AP-237 is 68–156 times less potent than fentanyl—fentanyl is approximate 100 more potent than morphine. Both Vandeputte and Volpe caution against using binding affinity exclusively to compare potency. Moreover, studies illustrate that compounds substituted with a cinnamyl group at the N4 of the piperazine ring in 1-acyl-4-substituted piperazines show potent analgesic activity. Notably, as of June 2021, 2-methyl-AP-237 has been linked to at least two fatal overdose deaths in the United States.

Furlan D (1985) Methyl-piperazino derivatives with analgesic activity, a process for their preparation, and therapeutic compounds which contain them. European Patent EP0142756A2. (available at https://patentimages.storage.googleapis.com/6e/68/90/c6cee 98b6b f926/EP0142756A 2.pdf) (last visited Dec. 20, 2021).

Vandeputte MM, Cannaert A, Stove CP. In vitro functional characterization of a panel of non-fentanyl opioid new psychoactive substances. Arch Toxicol. 94(11):3819-3830. (2020).

Resnik K, Brandao P, Amorim Alves E. DARK classics in chemical neuroscience: Bucinnazine. ACS Chem. Neurosci. 2021, 12, 3527–3534.

(4) The history and current pattern of abuse.

The illicit use of both AP-237 and 2-methyl-AP-237 was first detected in 2019. 2-methyl-AP-237 has been associated with at least two overdose fatalities since that time. Neither AP-237 nor 2-methyl-AP-237 is available for medical use in the United States. Because sources are unregulated, the identity, purity, and quantity of the illicit product is unknown and may be inconsistent posing adverse public health risks.

In a similar modus operandi as witnessed in the cases of synthetic cannabinoids and substituted cathinones, substances sold as "designer opioids"—including AP-237 and 2-

[4] 2-Methyl-AP-237 was originally patented in 1985.

methyl-AP-237—are available on the internet. As the opioid crisis has evolved, iatrogenic comorbidity involving benzodiazepines and available opioids has become a growing concern. Consistent with this pattern of opioid abuse, 2-methyl-AP-237 has been detected in at least one toxicology sample that was also found to contain etizolam.

Drug Fact Sheet: 2-Methyl-AP-237. Drug Enforcement Administration. (available at https://www.deadiversion.usdoj.gov/drug_chem_info/2-Methyl-AP-237.pdf) (last visited Dec. 20, 2021).

Resnik K, Brandao P, Amorim Alves E. DARK classics in chemical neuroscience: Bucinnazine. ACS Chem. Neurosci. 2021, 12, 3527–3534.

Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, Mackey S. Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis. BMJ 356:j760 (available at https://doi.org/10.1136/bmj.j760) (2017).

(5) The scope, duration, and significance of abuse.

The scope, duration, and significance of opioid abuse is well-characterized. Illicitly available NSOs deviate from the classical fentanyl and morphinan chemical structures. The vast variety of molecular modifications render the identification of NSOs in both drug seizure and toxicology evidence arduous.

Even when NSOs can be identified, like other non-controlled substances, precisely determining the scope of abuse is a challenge. Laboratories either do not target their analysis for the identification of the non-controlled substance or the reported findings are, "no controlled substance found."

Nonetheless, it is known that as opioid abuse continues to rise, so too do efforts by clandestine chemists to synthesize and distribute NSOs that skirt chemical control policies. Following the pattern of other NPSs before them, AP-237 and 2-methyl-AP-237 are a public health concern that may well grow without effective counter-control measures.

Jones CM, Logan J, Gladden RM, Bohm MK. Vital Signs: Demographic and Substance Use Trends Among Heroin Users - United States, 2002-2013. MMWR Morb Mortal Wkly Rep. 2015 Jul 10;64(26):719-25.

Resnik K, Brandao P, Amorim Alves E. DARK classics in chemical neuroscience: Bucinnazine. ACS Chem. Neurosci. 2021, 12, 3527–3534.

Vandeputte MM, Cannaert A, Stove CP. In vitro functional characterization of a panel of non-fentanyl opioid new psychoactive substances. Arch Toxicol. 94(11):3819-3830. (2020).

(6) The risk to the public health.

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Synthetic opioids are the primary cause of overdose deaths in the United States. Indeed, in its December 7, 2021 Notice of Intent to Schedule, the DEA stated that, "[t]rafficking, continued evolution, and abuse of new synthetic opioids are deadly trends posing imminent hazards to public safety." As of June 2021, 2-methyl-AP-237 has been linked to at least two fatal overdose deaths in the United States. Moreover, because sources are unregulated, the identity, purity, and quantity of the illicit product is unknown and may be inconsistent posing adverse public health risks.

Resnik K, Brandao P, Amorim Alves E. DARK classics in chemical neuroscience: Bucinnazine. ACS Chem. Neurosci. 2021, 12, 3527–3534.

Schedules of Controlled Substances: Temporary Placement of Butonitozene, Etodesnitazene, Flunitazene, Metodesnitazene, Metonitazene, N-pyrrolidino etonitazene, and Protonitazene in Schedule I; Drug Enforcement Administration; 86 Fed. Reg. 69,182 (Dec. 7, 2021).

Drug Fact Sheet: 2-Methyl-AP-237. Drug Enforcement Administration. (available at https://www.deadiversion.usdoj.gov/drug_chem_info/2-Methyl-AP-237.pdf) (last visited Dec. 20, 2021).

(7) The potential of the substance to produce psychic or physiological dependence liability; and

Among other effects, mu-opioid receptors are responsible for physical dependence. Most opioid analgesic and anesthetic drugs have significant mu-opioid receptor agonist activity. AP-237 and 2-methyl-AP-237 have pharmacological profiles similar to the mu-opioid agonist-like activity of a classical opioid.

Volpe DA, McMahon Tobin GA, Mellon RD, Kadki AG, Parker RJ, Colatsky T, Kropp TJ, Verbois SL (2011). Uniform assessment and ranking of opioid Mu receptor binding constants for selected opioid drugs. Reg. Tox. and Pharm. 59(2011) 385–390.

(8) Whether the substance is an immediate precursor.

Neither AP-237 nor 2-methyl-AP-237 is known to be an immediate precursor.

Section 5: Finding of the Board

Section 3719.44 of the Ohio Revised Code authorizes that the State of Ohio Board of Pharmacy may add or transfer a compound, mixture, preparation, or substance to schedule I when it appears that there is a high potential for abuse, that it has no accepted medical use in treatment in this state, or that it lacks accepted safety for use in treatment under medical supervision.

After a thorough review of all available data, the State of Ohio Board of Pharmacy finds that each AP-237 and 2-methyl-AP-237:

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1. Has a high potential for abuse;
2. Has no accepted medical use in treatment in this state;
3. Lacks accepted safety for use in treatment under medical supervision;
4. Follows the same history and pattern of abuse as other schedule I mu-opioid receptor agonists;
5. Poses a risk to the public health of the citizens in this state; and
6. Has an associated physiological dependence liability.

Based on these findings, the Board hereby concludes that AP-237 and 2-methyl-AP-237 be controlled in Schedule I and authorizes the filing of amended rule 4729:9-1-01 of the Administrative Code that was approved on **DATE**.