U.S. Department of Justice
Drug Enforcement Administration
Office of Forensic Sciences

The U.S. Attorney General has determined that the publication of this periodical is necessary in the transaction of the public business required by the Department of Justice. Information, instruction, and disclaimers are published in the January issues.

– NOVEMBER 2011 –

– SCHEDULING UPDATE –

[Editor's Preface: The following notice has been edited for Microgram Bulletin. See the Federal Register: October 21, 2011 (Volume 76, Number 204) (Rules and Regulations) (Pages 65371-65375) for the complete text.]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-357]

Schedules of Controlled Substances: Temporary Placement of Three Synthetic Cathinones Into Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final Order.

SUMMARY: The Administrator of the Drug Enforcement Administration (DEA) is issuing this final order to temporarily schedule three synthetic cathinones under the Controlled Substances Act (CSA) pursuant to the temporary scheduling provisions of **21 U.S.C. 811**(h). The substances are 4-methyl-N-methylcathinone (mephedrone), 3,4-methylenedioxy-N-methylcathinone (methylone), and 3,4-methylenedioxypyrovalerone (MDPV). This action is based on a finding by the Administrator that the placement of these synthetic cathinones and their salts, isomers, and salts of isomers into Schedule I of the CSA is necessary to avoid an imminent hazard to the public safety. As a result of this order, the full effect of the CSA and its implementing regulations including criminal, civil and administrative penalties, sanctions and regulatory controls of Schedule I substances will be imposed on the manufacture, distribution, possession, importation, and exportation of these synthetic cathinones.

DATES: Effective Date: This Final Order is effective on October 21, 2011.

FOR FURTHER INFORMATION CONTACT: Imelda L. Paredes, Office of Diversion Control, Drug Enforcement Administration, 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone (202) 307-7165.

SUPPLEMENTARY INFORMATION:

Background

The Comprehensive Crime Control Act of 1984 (Pub. L. 98-473), which was signed into law on October 12, 1984, amended section 201 of the CSA (**21 U.S.C. 811**) to give the Attorney General the authority to temporarily place a substance into Schedule I of the CSA for one year without regard to the requirements of 21 U.S.C. 811(b) if he finds that such action is necessary to avoid imminent hazard to the public safety, 21 U.S.C. 811(h); **21 CFR 1308.49**. If proceedings to control a substance are initiated under 21 U.S.C. 811(a)(1), the Attorney General may extend the temporary scheduling up to an additional six months, 21 U.S.C. 811(h)(2). Where the necessary findings are made, a substance may be temporarily scheduled in Schedule I if it is not listed in any other schedule under section 202 of the CSA (**21 U.S.C. 812**) or if there is no exemption or approval in effect under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) for the substance, 21 U.S.C. 811(h)(1). The Attorney General has delegated his authority under 21 U.S.C. 811 to the Administrator of DEA, 28 CFR 0.100.

Section 201(h)(4) of the CSA (**21 U.S.C. 811**(h)(4)) requires the Administrator to notify the Secretary of Health and Human Services of her intention to temporarily place a substance into Schedule I of the CSA.\1\

The Administrator transmitted notice of her intent to place mephedrone, methylone and MDPV in Schedule I on a temporary basis to the Assistant Secretary in a letter dated June 15, 2011. The Assistant Secretary responded to this notice by letter dated July 25, 2011, and advised that based on review by the Food and Drug Administration (FDA) there are currently no investigational new drug applications (INDs) or approved new drug applications (NDAs) for MDPV, mephedrone, or methylone. The Assistant Secretary also stated that the Department of Health and Human Services has no objection to the temporary placement of MDPV, mephedrone, and methylone into Schedule I of the CSA. DEA has taken into consideration the Assistant Secretary's comments. As MDPV, mephedrone, and methylone are not currently listed in any schedule under the CSA, as no exemptions or approvals are in effect for MDPV, mephedrone, and methylone under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), and as this temporary scheduling is necessary to avoid an imminent hazard to the public safety, DEA believes that the conditions of **21 U.S.C. 811**(h)(1) have been satisfied.

[\1\ Because the Secretary of Health and Human Services has delegated to the Assistant Secretary for Health of the Department of Health and Human Services the authority to make domestic drug scheduling recommendations, for purposes of this Final Order, all subsequent references to "Secretary" have been replaced with "Assistant Secretary."]

A notice of intent to temporarily place mephedrone, methylone, and MDPV into Schedule I of the CSA was published in the Federal Register on September 8, 2011 (76 FR 55616). The data in support of the notice of intent and additional data continue to support the necessary findings to place mephedrone, methylone, and MDPV temporarily into Schedule I of the CSA as necessary to avoid an imminent hazard to the public safety.\2\ In making this finding, the Administrator is required to consider three of the eight factors set forth in section 201(c) of the CSA (**21 U.S.C. 811**(c)). These factors are as follows: The substance's history and current pattern of abuse; the scope, duration and significance of abuse; and what, if any, risk there is to the public health, 21 U.S.C. 811(c)(4)-(6). Consideration of these factors includes actual abuse, diversion from legitimate channels, and clandestine importation, manufacture, or distribution, 21 U.S.C. 811(h)(3).

[\2\ See "Background, Data and Analysis of Synthetic Cathinones: Mephedrone (4-MMC), Methylone (MDMC) and 3,4-Methylenedioxy-pyrovalerone (MDPV)" found at http://www.regulations.gov.]

Mephedrone, methylone, and MDPV are not currently listed in any schedule under the CSA. The temporary placement of these three synthetic cathinones into Schedule I of the CSA is necessary in order to avoid an imminent hazard to the public safety. First, there has been a rapid and significant increase in abuse of these substances in the United States. As a result of this abuse, synthetic cathinones are banned in at least 37 states in the United States and several countries, and all five branches of the U.S. military prohibit military personnel from possessing or using synthetic cathinones. Second, law enforcement has seized synthetic cathinones and, based on self-reports to law enforcement and health care professionals, synthetic cathinones are abused for their psychoactive properties. Third, federal, state and local public health departments and poison control centers have issued reports describing public health consequences such as emergency department visits and deaths from the use of these synthetic cathinones. Based on scientific data currently available, these three substances have the potential to be extremely harmful and, therefore, pose an imminent hazard to the public safety.

Factor 4: History and Current Pattern of Abuse

Synthetic cathinones are designer drugs of the phenethylamine class which are structurally and pharmacologically similar to amphetamine, 3,4-methylenedioxymethamphetamine (MDMA), cathinone, and other related substances. The addition of a beta-keto ([beta]-keto) substituent to the phenethylamine core structure produces a group of substances that now have cathinone as the core structure. Synthetic cathinones, like amphetamine, cathinone, methcathinone, and methamphetamine, are central nervous system (CNS) stimulants.

The synthetic cathinones mephedrone, methylone, and MDPV have recently emerged on the United States' illicit drug market and are being perceived as being 'legal' alternatives to cocaine, methamphetamine, and MDMA. Although synthetic cathinones are new to the United States' illicit drug market, they have been popular drugs of abuse in Europe since 2007. MDPV is a derivative of pyrovalerone, which is a psychoactive drug that was used to treat chronic lethargy and fatigue. Research in anti-depressant and anti-parkinson agents resulted in the development and patenting of methylone. Methylone, however, has not been approved for these purposes. There are no currently accepted medical uses in treatment in the United States for mephedrone, methylone, or MDPV.

Mephedrone, methylone, and MDPV are falsely marketed as "research chemicals," "plant food," or "bath salts." They are sold at smoke shops, head shops, convenience stores, adult book stores, and gas stations. They can also be purchased on the Internet and mailed using the U.S. Postal Service or international mail services. The packages of products containing these synthetic cathinones usually have the warning "not for human consumption," most likely in an effort to circumvent statutory restrictions for these substances. Despite disclaimers that the products are not intended for human consumption, retailers promote that routine urinalysis drug tests will not typically detect the presence of these synthetic cathinones. However, analytical methods for the detection of mephedrone, methylone, MDPV, and other synthetic cathinones have recently been developed for these substances.
Evidence indicates that mephedrone, methylone, and MDPV are being abused for their psychoactive properties. Drug surveys found that these and other synthetic cathinones are being used as recreational drugs and are used as alternatives to illicit stimulants like MDMA and cocaine. Accordingly, mephedrone, methylone, and MDPV have been identified in human urine samples that were obtained for routine drug screenings, they have been detected in samples from drivers suspected of driving under the influence, and they have been detected by drug courts during mandatory periodic drug screens. They have also been identified in biological specimens from individuals (some exhibiting symptoms of "extreme agitation" or "excited delirium") who have been arrested for possession of a controlled substance, child endangerment, or homicide. They have been detected in samples from decedents whose causes of death were reported as drug-induced toxicity, multiple drug toxicity, or other causes (e.g., blunt force trauma from a vehicular collision or suicide).

Based on studies in the scientific literature, the marketing of products that contain mephedrone, methylone, and MDPV is geared towards teens and young adults. Accordingly, reports indicate that the main users of synthetic cathinones are young male adults. These substances are also used by mid-to-late adolescents and older adults. Many of these abusers of synthetic cathinones have a previous history of drug abuse.

According to drug surveys, the reported average amount of synthetic cathinones used per dose ranged from approximately 25 to 250 milligrams and the average amount used per session (i.e., repeated administration and binging) ranged from approximately 25 milligrams to 5 grams depending on the substance consumed, duration of intake, and route of administration. The most common routes of administration of these substances are nasal insufflation by snorting the powder and oral ingestion by swallowing capsules or tablets. Other reported methods of administration include injection, rectal administration, and "bombing" (wrapping a dose of powder in a paper wrap and swallowing). Synthetic cathinones have also been reported to be used in binges. Reasons cited for binging include to prolong the duration of effects, to satisfy a "craving," or to satisfy a strong urge to re-dose.

According to information found in drug surveys, clinical case reports, and law enforcement reports, users have reported using products containing mephedrone, methylone, and MDPV with other synthetic cathinones (e.g., butylone, fluoromethcathinone, 4-MEC, etc.), pharmaceutical agents (e.g., lidocaine, caffeine, benzocaine, etc.), or other recreational substances (e.g., amphetamine, MDMA, cocaine, gamma-butyrolactone (GBL), kratom, N-benzylpiperazine (BZP), and 1-(3-trifluoromethylphenyl)-piperazine (TFMPP)). Chemical analyses of seized and purchased synthetic cathinone products indicate that some products contain multiple substances. Furthermore, investigative toxicology reports of drug screens in which more than one substance was detected indicate that users have ingested products composed of drug combinations (e.g., a tablet composed of MDPV and BZP) or multiple drug products (e.g., a MDPV powder product and a MDMA tablet).

Factor 5: Scope, Duration and Significance of Abuse

The popularity of synthetic cathinones as recreational drugs has increased since they first appeared on the United States' illicit drug market. According to forensic laboratory reports, the first appearance of these synthetic cathinones in the United States occurred in 2009. In 2009, NFLIS registered 15 exhibits from 8 states containing these three synthetic cathinones. In 2010, there were 574 reports from 29 states related to these substances registered in NFLIS, and in 2011 (January to August) there were 995.\3\

[\3\ Analyzed on September 15, 2011.]

Based on reports to DEA from law enforcement and public health officials, synthetic cathinones are becoming increasingly prevalent and abused throughout the United States. At one United States point of entry, the U.S. Customs and Border Protection (CBP) has encountered at least 127 shipments containing primarily mephedrone, methylone, and MDPV, as well as other synthetic cathinones like 4-MEC, butylone, fluoromethcathinone, and dimethylcathinone. Most of these shipments originated in China or India and were being shipped to destinations throughout the United States such as Arizona, Alaska, Hawaii, Kansas, Louisiana, Oklahoma, Oregon, Pennsylvania, Missouri, Virginia, Washington, and West Virginia. The American Association of Poison Control Centers (AAPCC), a non-profit, national organization that represents the poison control centers of the United States, reported that in 2010, poison control centers took 303 calls about synthetic cathinones. However, in just the first eight months of 2011, poison control centers have already received 4,720 calls relating to these products. These calls were received in poison control centers representing at least 47 states and the District of Columbia. Individual state poison control centers have also reported an increase in the number of calls regarding "bath salts" from 2009 to 2011.

Concerns over the abuse of these and other synthetic cathinones have prompted many states to control these substances. As of September 15, 2011, at least 37 states have emergency scheduled or enacted legislation placing regulatory controls on some or many of the synthetic cathinones. These states include Alabama, Arkansas, Connecticut, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Michigan, Minnesota, Mississippi, Missouri, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Texas, Tennessee, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin and Wyoming. Several countries including all members of the European Union have also placed controls on the possession and/or sale of one or more of these substances. Moreover, the use of synthetic cathinones by members of the U.S. Armed Forces is prohibited.

Factor 6: What, if Any, Risk There Is to the Public Health

The risks to the public health associated with the abuse of mephedrone, methylone, and MDPV relate to acute and long term public health and safety problems. These synthetic cathinones have become a serious drug abuse threat as there have been reports of emergency room admissions and deaths associated with the abuse of these substances.

Clinical case reports indicate that these synthetic cathinones produce a number of stimulant-like adverse effects such as palpitation, seizure, vomiting, sweating, headache, discoloration of the skin, hypertension, and hyper-reflexia. Adverse effects associated with consumption of these drugs as reported by abusers include nose-bleeds, bruxism (teeth grinding), paranoia, hot flashes, dilated pupils, blurred vision, dry mouth/thirst, palpitations, muscular tension in the jaw and limbs, headache, agitation, anxiety, tremor, and fever or sweating. Consequently, numerous individuals have presented at emergency departments in response to exposure incidents and several cases of acute toxicity have been reported due to the ingestion of mephedrone, methylone, or MDPV. In addition, case reports have shown that the abuse of synthetic cathinones can lead to psychological dependence like that reported for other stimulant drugs.

According to clinical case reports, investigative toxicological reports, and autopsy reports, mephedrone, methylone, and MDPV have been implicated in drug induced overdose deaths. In at least three reported deaths, one of these synthetic cathinones was ruled as the cause of death. Other deaths involved individuals under the influence of these synthetic cathinones who acted violently and unpredictably in causing harm to themselves or others. There have also been reports in the scientific literature of deaths caused by individuals who were driving under the influence of these synthetic cathinones.

A number of synthetic cathinones and their products, as identified by CBP and reported in the scientific literature, appear to originate from foreign sources. The manufacturers and retailers who make and sell these products do not fully disclose the product ingredients including the active ingredients or the health risks and potential hazards associated with these products. This poses significant risk to abusers who may not know what they are purchasing or the risk associated with the use of those products.

Based on the above data, the continued uncontrolled manufacture, distribution, importation, exportation, and abuse of mephedrone, methylone, and MDPV pose an imminent hazard to the public safety. DEA is not aware of any recognized therapeutic uses of these synthetic cathinones in the United States.

DEA has considered the three criteria for placing a substance into Schedule I of the CSA (**21 U.S.C. 812**), and finds that the data available and reviewed for mephedrone, methylone, and MDPV indicate that these synthetic cathinones each have a high potential for abuse, no currently accepted medical use in treatment in the United States, and lack accepted safety for use under medical supervision.

In accordance with the provisions of section 201(h) of the CSA (**21 U.S.C. 811**(h)) and 28 CFR 0.100, the Administrator has considered the available data and the three factors required to support a determination to temporarily schedule three synthetic cathinones (4-methyl-N-methylcathinone, 3,4-methylenedioxy-N-methylcathinone, and 3,4-methylenedioxypyrovalerone) in Schedule I of the CSA and finds that placement of these synthetic cathinones and their salts, isomers, and salts of isomers into Schedule I of the CSA is necessary to avoid an imminent hazard to the public safety.

Regulatory Requirements

[Editor's Note: See the Federal Register for the Regulatory Requirements.]

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

Under the authority vested in the Attorney General by section 201(h) of the CSA (**21 U.S.C. 811**(h)), and delegated to the Administrator of the DEA by Department of Justice regulations (28 CFR 0.100), the Administrator hereby orders that **21 CFR Part 1308** be amended as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

1. The authority citation for Part 1308 continues to read as follows:

Authority: **21 U.S.C. 811**, **812**, **871**(b), unless otherwise noted.

2. **Section 1308.11** is amended by adding new paragraphs (g)(6), (7) and (8) to read as follows:

Sec. 1308.11 Schedule I.

* * * * *

(g) * * *

(6) 4-methyl-N-methylcathinone--1248
(Other names: mephedrone)
(7) 3,4-methylenedioxy-N-methylcathinone--7540
(Other names: methylone)
(8) 3,4-methylenedioxypyrovalerone--7535
(Other names: MDPV)

* * * * *

Dated: October 14, 2011.

Michele M. Leonhart,
Administrator.

[FR Doc. 2011-27282 Filed 10-20-11; 8:45 am]

BILLING CODE 4410-09-P

– PROPOSED RULE –

[Editor's Preface: The following notice has been edited for Microgram Bulletin. See the Federal Register: October 21, 2011 (Volume 76, Number 204) (Proposed Rules) (Pages 65424-65428) for the complete text.]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-354]

Schedules of Controlled Substances: Placement of Ezogabine Into Schedule V

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Drug Enforcement Administration (DEA) proposes placing the substance ezogabine, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible, into Schedule V of the Controlled Substances Act (CSA). This proposed action is pursuant to the CSA which requires that such actions be made on the record after opportunity for a hearing through formal rulemaking.

DATES: DEA will permit interested persons to file written comments on this proposal pursuant to **21 CFR 1308.43**(g). Electronic comments must be submitted and written comments must be postmarked on or before November 21, 2011. Commenters should be aware that the electronic Federal Docket Management System will not accept comments after midnight Eastern Time on the last day of the comment period.

Interested persons, defined as those "adversely affected or aggrieved by any rule or proposed rule issuable pursuant to section 201 of the Act (**21 U.S.C. 811**)," \1\ may file a request for hearing pursuant to **21 CFR 1308.44** and in accordance with **21 CFR 1316.45** and **1316.47**. Requests for hearing, notices of appearance, and waivers of participation must be received on or before November 21, 2011.

[\1\ **21 CFR 1300.01**.]

ADDRESSES: To ensure proper handling of comments, please reference "Docket No. DEA-354" on all electronic and written correspondence. DEA encourages all comments be submitted electronically through http://www.regulations.gov using the electronic comment form provided on that site. An electronic copy of this document and supplemental information to this proposed rule are also available at the http://www.regulations.gov Web site for easy reference. Paper comments that duplicate the electronic submission are not necessary as all comments submitted to http://www.regulations.gov will be posted for public review and are part of the official docket record. Should you, however, wish to submit written comments via regular or express mail, they should be sent to the Drug Enforcement Administration, Attention: DEA Federal Register Representative/OD, 8701 Morrissette Drive, Springfield, VA 22152. All requests for hearing must be sent to Drug Enforcement Administration, Attention: Hearing Clerk/LJ, 8701 Morrissette Drive, Springfield, VA 22152.

FOR FURTHER INFORMATION CONTACT: Rhea D. Moore, Office of Diversion Control, Drug Enforcement Administration, 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone (202) 307-7165.

SUPPLEMENTARY INFORMATION:

Posting of Public Comments: Please note that all comments received are considered part of the public record and made available for public inspection online at http://www.regulations.gov and in the DEA's public docket. Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter.

If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want it to be posted online or made available in the public docket, you must include the phrase

"PERSONAL IDENTIFYING INFORMATION" in the first paragraph of your comment. You must also place all of the personal identifying information you do not want posted online or made available in the public docket in the first paragraph of your comment and identify what information you want redacted.

If you want to submit confidential business information as part of your comment, but do not want it to be posted online or made available in the public docket, you must include the phrase "CONFIDENTIAL BUSINESS INFORMATION" in the first paragraph of your comment. You must also prominently identify confidential business information to be redacted within the comment. If a comment has so much confidential business information that it cannot be effectively redacted, all or part of that comment may not be posted online or made available in the public docket.

Personal identifying information and confidential business information identified and located as set forth above will be redacted, and the comment, in redacted form, will be posted online and placed in the DEA's public docket file. Please note that the Freedom of Information Act applies to all comments received. If you wish to inspect the agency's public docket file in person by appointment, please see the "For Further Information" paragraph.

Request for Hearing, Notice of Appearance at or Waiver of Participation in Hearing

[Editor's Note: See the Federal Register for information on Requests for Hearing, Notice of Appearance at or Waiver of Participation in Hearing.]

Legal Authority

[Editor's Note: See the Federal Register for the Legal Authority.]

Background

Ezogabine, known chemically as N-[2-amino-4-(4-fluorobenzylamino)-phenyl]-carbamic acid ethyl ester, is a new chemical substance with central nervous system depressant properties and is classified as a sedative-hypnotic. Pharmacological studies indicate that ezogabine primarily acts as a ligand at ion-gated channels in the brain to enhance potassium currents mediated by neuronal KCNQ (Kv7) channels. Additionally, ezogabine indirectly enhances the gamma-aminobutyric acid (GABA) mediated neurotransmission. On June 10, 2011, the Food and Drug Administration (FDA) approved a New Drug Application (NDA) for ezogabine as an adjunct treatment of partial onset seizures, to be marketed under the trade name Potiga.\2\

[\2\ http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022345Orig1s000TOC.cfm; as of July 21, 2011.]

Proposed Determination to Schedule Ezogabine

Pursuant to **21 U.S.C. 811**(a), proceedings to add a drug or substance to those controlled under the CSA may be initiated by request of the Secretary of HHS. On January 12, 2011, HHS provided DEA with a scientific and medical evaluation document prepared by FDA entitled "Basis for the Recommendation for Control of Ezogabine in Schedule V of the Controlled Substances Act." Pursuant to 21 U.S.C. 811(b), this document contained an eight-factor analysis of the abuse potential of ezogabine as a new drug, along with HHS' recommendation to control ezogabine under Schedule V of the CSA.

In response, DEA conducted an eight-factor analysis of ezogabine's abuse potential pursuant to **21 U.S.C. 811**(c). Included below is a brief summary of each factor as analyzed by HHS and DEA, and as considered by DEA in the scheduling decision. Please note that both the DEA and HHS analyses are available in their entirety under "Supporting and Related Material" of the public docket for this rule at www.regulations.gov under docket number DEA-354.

1. The Drug's Actual or Relative Potential for Abuse: Ezogabine is a new chemical substance that has not been marketed in the U.S. or in any other country. As such, there is no information available which details actual abuse of ezogabine. However, the legislative history of the CSA offers another methodology for assessing a drug or substance's potential for abuse:

> The drug or drugs containing such a substance are new drugs so related in their action to a drug or drugs already listed as having a potential for abuse to make it likely that the drug will have the same

potentiality for abuse as such drugs, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.\3\

[\3\ Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970); 1970 U.S.C.C.A.N. 4566, 4601.]

Ezogabine acts as a ligand at ion-gated channels in the brain, similar to the Schedule V substances pregabalin and lacosamide, and, like those drugs, ezogabine is indicated for the treatment of epileptic conditions in humans. There is strong evidence, described below, that ezogabine produces behavioral effects in humans and in animals that are similar to those produced by pregabalin and lacosamide.

Phase 1 clinical studies indicate that the rate of euphoria-related adverse events (AEs) resulting from administration of ezogabine was 6-9%. This is similar to the AE rates for administration of pregabalin (10%) and lacosamide (>7%), while Phase \2/3\ clinical studies indicated similar AE rates between ezogabine (<1%) and lacosamide (<2%). Animal studies involving administration of ezogabine to animals produced a sedative behavioral profile similar to that produced from administration of pregabalin and lacosamide, including decreased locomotion, decreased muscle tone, and an increase in ataxia. Further, in abuse potential studies conducted with sedative-hypnotic abusers, ezogabine, pregabalin, and lacosamide, when compared to placebos, are similar in their ability to produce statistically significant increases in subjective responses including "Drug Liking," "Euphoria," "Overall Drug Liking," "Good Drug Effects," and "High."
Because of the similarities between ezogabine, pregabalin, and lacosamide, it is very likely that ezogabine will have an abuse potential similar to those Schedule V substances. Currently there is a lack of evidence regarding the diversion, illicit manufacturing or deliberate misuse of ezogabine due to its commercial unavailability in any country, but since ezogabine is not readily synthesized from available substances, any diversion would be from legitimate channels. The above referenced studies, which include demonstration of the significant euphoric effects produced by ezogabine in humans, predict that there will be significant use of ezogabine contrary to or without medical advice.

2. Scientific Evidence of the Drug's Pharmacological Effects, If Known: Ezogabine acts to enhance potassium currents mediated by neuronal KCNQ (Kv7) channels with a secondary action through the augmentation of GABA -mediated neurotransmission without direct GABA receptor stimulation. In individuals with histories of recreational sedative-hypnotic abuse, ezogabine (300 and 600 mg orally) produced increased ratings on the primary positive subjective scales [VAS-Drug-liking, VAS-Overall Drug Liking, ARCI-MBG (Euphoria), VAS-Take Drug Again] for peak responses (Emax for the first eight hours after drug administration) that were significantly different from the placebo. This effect is similar to that produced by alprazolam (1.5 and 3.0 mg orally; Schedule IV). On secondary positive subjective scales [VAS-High, VAS-Good Effects, ARCI-Amphetamine (Activation)] for peak responses, both ezogabine and alprazolam produced significant increases compared to the placebo, while there were no differences between ezogabine and alprazolam on those measures.

In human abuse potential studies, ezogabine (300 and 600 mg), upon oral administration, increased ratings on negative and sedating subjective measures [VAS-Bad Effects, ARCI-LSD (dysphoria) and ARCI-PCAG (sedation)] compared to the placebo, but these increases were lower than those produced by 1.5 and 3.0 mg alprazolam. These data for ezogabine are similar to those produced by lacosamide. A 900 mg dose of ezogabine produced VAS-Drug Liking and VAS-Good Effects that were higher than those produced by the two lower doses of ezogabine and either dose of alprazolam. However, the changes in VAS-Bad Effects and ARCI-LSD (dysphoria) following 900 mg ezogabine were less than or similar to those produced by lower doses of ezogabine and either dose of alprazolam. The adverse events following 900 mg ezogabine are similar to those described in the NDA for the human abuse potential study conducted with lacosamide. These included euphoria, somnolence, visual disturbances, and altered auditory perception.

In human abuse potential studies, ezogabine, similar to pregabalin and lacosamide, also produced ratings on each of the positive subjective responses that were statistically similar to those produced by Schedule IV benzodiazepines (alprazolam or diazepam). Although this appears to suggest that these drugs have an abuse potential similar to that of Schedule IV substances, the other data from human abuse potential studies, the adverse effect profile data from safety and efficacy studies, and the data from the preclinical animal behavioral studies demonstrate that ezogabine has abuse potential less than that of Schedule IV drugs but similar to that of Schedule V drugs.

3. The State of Current Scientific Knowledge Regarding the Drug or Other Substance: The chemical name of ezogabine is N-[2-amino-4-(4-fluorobenzylamino)-phenyl]-carbamic acid ethyl ester. It is an achiral molecule with a molecular formula of $C_{16}H_{18}FN_3O_2$ and a molecular weight of 303.3 g/mol. Ezogabine is a non-hygroscopic white to slightly colored powder with a melting point of 140-143°C. It is soluble in 0.9% saline, methanol, chloroform, but only sparingly soluble in ethanol and 0.1N HCl.

Ezogabine in humans has a T_{max} (time required for ezogabine to reach maximum plasma concentration) ranging from 1-4 hours following both acute and multiple dosing, and, without the involvement of cytochrome P450, undergoes an extensive and almost exclusively phase 2 metabolic biotransformation. Ezogabine is predominantly metabolized by N-glucuronidation, resulting in the formation of two distinct N-glucuronides of the unchanged parent drug and to a lesser extent by N-acetylation to form N-acetyl-retigabine, the major bioactive metabolite of ezogabine. The half-life of both ezogabine and N-acetyl-retigabine is approximately eight hours and the C_{max} (maximum plasma concentration) of both components is dose proportional after both acute and multiple dosing, suggesting a lack of accumulation with repeated administration.

4. Its History and Current Pattern of Abuse: As stated in the summary of Factor 1, information on ezogabine's history and current pattern of abuse is unavailable as it has not been marketed in any country. As such, evaluation of abuse potential for ezogabine derives from positive indicators in clinical studies which are believed to be predictive of drug abuse and which are discussed in Factors 1 and 2 above.

5. The Scope, Duration, and Significance of Abuse: Because ezogabine has not been marketed in any country, information on the scope, duration, and significance of abuse of ezogabine is unavailable. However, epidemiological data on pregabalin, a Schedule V drug with an abuse potential similar to that of ezogabine, is available from the Drug Abuse Warning Network (DAWN) database.

The "abuse frequency ratio," calculated as the ratio of nonmedical use related annual emergency department visits (as reported in DAWN) to the total number of annual prescriptions for pregabalin is less than that for the Schedule IV drug, alprazolam. Further, because ezogabine has abuse-related human and animal data in its NDA similar to data generated for pregabalin, ezogabine is likely to have an abuse potential similar to pregabalin. The "abuse frequency ratios" for pregabalin range from 29 to 47, while those for alprazolam are approximately three to six times higher, ranging from 160 to 235. Thus, pregabalin was placed into Schedule V based both on abuse-related human and animal data submitted in its NDA and by epidemiological data which justified placement relative to drugs in Schedule IV. Given that ezogabine has abuse-related human and animal data in its NDA similar to the data generated by pregabalin, it is likely that ezogabine will have an abuse potential similar to this Schedule V drug.

6. What, if any, Risk There is to the Public Health: The data indicates that ezogabine may present a serious safety risk to the public health, and the predicted level of risk is similar to that observed with pregabalin and lacosamide but less than that produced by Schedule IV benzodiazepines. In Phase 1 clinical safety studies, the overall adverse event profile following ezogabine administration was similar to those from pregabalin and lacosamide and includes not only euphoria, but also somnolence, and feeling or thinking abnormally. Further, the human abuse potential study showed that the majority of subjects receiving the 900 mg dose of ezogabine experienced multiple adverse events such as euphoria, somnolence, visual disturbance, amnesia, hypo-aesthesia, paranoia, fear, confusion and hallucination. Although the 900 mg dose is three times greater than the recommended therapeutic dose, individuals who abuse drugs typically do so at supra-therapeutic doses.

7. Its Psychic or Physiological Dependence Liability: Ezogabine may produce limited psychic or physiological dependence liability following extended administration. Since there are no studies detailing abrupt discontinuation of ezogabine, there are minimal adequate data to evaluate the ability of ezogabine to induce withdrawal symptoms that are indicative of physical dependence. Many of the adverse events reported from the discontinuation of ezogabine were also reported prior to its discontinuation, including dizziness, somnolence, and a state of confusion. By comparison, abrupt or rapid discontinuation of pregabalin in human studies resulted in patient-reported symptoms of nausea, headache or diarrhea, which are suggestive of physical dependence, while abrupt termination of lacosamide produced no signs or symptoms of withdrawal in diabetic neuropathic pain patients.

Unlike ezogabine and pregabalin, the withdrawal syndrome following discontinuation of Schedule IV substances such as alprazolam can range from mild dysphoria and insomnia to a major syndrome including abdominal pain, muscle cramps, vomiting, sweating, tremors and convulsions. These are similar in character to those associated with other sedative-hypnotics.

The study of ezogabine abuse potential in humans with histories of recreational abuse of sedative-hypnotics found that ezogabine produces euphoria (18-33%) in these individuals. Additionally, ezogabine produced euphoria (8.5%) in Phase 1 studies in healthy individuals. These euphoria-related adverse events following administration of ezogabine are suggestive of its ability to produce psychic dependence, and the adverse events appear to be less severe and occur less frequently than Schedule IV drugs (diazepam and alprazolam) and are more similar to those of Schedule V drugs, pregabalin and lacosamide.

8. Whether the Substance is an Immediate Precursor of a Substance Already Controlled Under the CSA: Ezogabine is not an immediate precursor of any controlled substance.

Conclusion: Based on consideration of the scientific and medical evaluation and accompanying recommendation of HHS, and based on DEA's consideration of its own eight-factor analysis, DEA finds that these facts and all relevant data constitute substantial evidence of potential for abuse of ezogabine. As such, DEA hereby proposes to schedule ezogabine as a controlled substance under the CSA.

Proposed Determination of Appropriate Schedule

The CSA establishes five schedules of controlled substances known as Schedules I, II, III, IV, and V. The statute outlines the findings required to place a drug or other substance in any particular schedule. **21 U.S.C. 812**(b). After consideration of the analysis and recommendation of the Assistant Secretary for Health of HHS and review of all available data, the Administrator of DEA, pursuant to 21 U.S.C. 812(b)(5), finds that:

(1) Ezogabine has a low potential for abuse relative to the drugs or other substances in Schedule IV. The overall abuse potential of ezogabine is comparable to the Schedule V substances such as pregabalin and lacosamide;

(2) Ezogabine has a currently accepted medical use in treatment in the United States. Ezogabine was approved for marketing by FDA as an adjunct treatment of partial onset seizures; and

(3) Abuse of ezogabine may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule IV.

Based on these findings, the Administrator of DEA concludes that ezogabine, including its salts, isomers and salts of isomers, whenever the existence of such salts, isomers, and salts of isomers is possible, warrants control in Schedule V of the CSA (**21 U.S.C. 812**(b)(5)).

Requirements for Handling Ezogabine

[Editor's Note: See the Federal Register for the Requirements for Handling Ezogabine.]

Regulatory Analyses

[Editor's Note: See the Federal Register for the Regulatory Analyses.]

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.
For the reasons set out above, 21 CFR part 1308 is proposed to be amended to read as follows:

PART 1308--SCHEDULES OF CONTROLLED SUBSTANCES

1. The authority citation for **21 CFR part 1308** continues to read as follows:
Authority: **21 U.S.C. 811**, **812**, **871**(b), unless otherwise noted.

2. **Section 1308.15** is amended by redesignating paragraphs (e)(1) and (2) as paragraphs (e)(2) and (3), and adding a new paragraph (e)(1) to read as follows:

Sec. 1308.15 Schedule V.
* * * * *
(e) * * *
(1) Ezogabine--2779
* * * * *

Dated: October 14, 2011.

Michele M. Leonhart,
Administrator.

[FR Doc. 2011-27253 Filed 10-20-11; 8:45 am]

BILLING CODE 4410-09-P

* *

SELECTED REFERENCES

[The Selected References section is a compilation of recent publications of presumed interest to forensic chemists. Unless otherwise stated, all listed citations are published in English. Abbreviated mailing address information duplicates that which is provided by the abstracting service. Patents and Proceedings are reported only by their *Chemical Abstracts* citation number. For full text copies of any of the articles listed, you may email the DEA Library at dea.library -at- usdoj.gov.]

1. Ali EMA, Edwards HGM, Scowen IJ. **Rapid in situ detection of street samples of drugs of abuse on textile substrates using microRaman spectroscopy.** Spectrochimica Acta, Part A: Molecular and Biomolecular Spectroscopy 2011;80(1): 2-7. [Editor's Notes: Presents title study. Contact: Raman Spectroscopy Group, Division of Chemical and Forensic Sciences, University of Bradford, Bradford BD7 1DP, United Kingdom.]

2. Emanuel CEJ, Ellison B, Banks CE. **Spice up your life: Screening the illegal components of 'Spice' herbal products.** Analytical Methods 2010;2(6):614-616. [Editor's Notes: Presents GC/MS and Solid Probe MS methods for the analysis of "Spice" related samples. Contact: Faculty of Science and Engineering, School of Biology, Chemistry and Health Science, Division of Chemistry and Materials, Manchester Metropolitan University, Manchester, UK M1 5GD, United Kingdom.]

3. Morrison C, Smith FJ, Tomaszewski T, Stawiarska K, Biziuk M. **Chiral gas chromatography as a tool for investigations into illicitly manufactured methylamphetamine.** Chirality 2011;23(7):519-522. [Editor's Notes: Presents a gas chromatographic method for the separation of the isomers of methamphetamine, ephedrine, pseudoephedrine, and the intermediates of the EMDE synthesis of methamphetamine. Contact: School of Science, University of the West of Scotland, Paisley, United Kingdom.]

4. Samms WC, Jiang YJ, Dixon MD, Houck SS, Mozayani A. **Analysis of alprazolam by DART-TOF mass spectrometry in counterfeit and routine drug identification cases.** Journal of Forensic Sciences 2011;56(4):993-998. [Editor's Notes: Presents title study. Contact: Harris County Institute of Forensic Sciences, Houston, TX 77054, USA.]

Additional References of Possible Interest:

1. Elsohly MA, Gul W, Elsohly KM, Murphy TP, Madgula VLM, Khan SI. **Liquid chromatography-tandem mass spectrometry analysis of urine specimens for K2 (JWH-018) metabolites.** Journal of Analytical Toxicology 2011;35(7):487-495. [Editor's Notes: Presents title study. Contact: ElSohly Laboratories, Inc., 5 Industrial Park Drive, Oxford, MS 38655, USA; National Center for Natural Products Research and Department of Pharmaceutics, The University of Mississippi, University, MS 38677, USA.]

2. Jin MJ, Jin C, Kim JY, In MK, Kwon OS, Yoo HH. **A quantitative method for simultaneous determination of 5-methoxy-N,N-diisopropyltryptamine and its metabolites in urine using liquid chromatography-electrospray ionization-tandem mass spectrometry.** Journal of Forensic Sciences 2011;56(4):1044-1048. [Editor's Notes: Presents title study. Contact: Doping Control Center, Korea Institute of Science and Technology, Seoul 130-650, South Korea.]

3. Mitrevski B, Wynne P, Marriott PJ. **Comprehensive two-dimensional gas chromatography applied to illicit drug analysis.** Analytical and Bioanalytical Chemistry 2011;401(8):2361-2371. [Editor's Notes: Presents a review of 2D GC analysis of illicit drugs. Contact: Centre for Green Chemistry, School of Chemistry, Monash University, VIC 3800, Australia.]

4. Prajapati P, Prajapati A. **Raman spectroscopy: A versatile tool in pharmaceutical analysis.** International Journal of Pharmaceutical Sciences Review and Research 2011;9(1):57-64. [Editor's Notes: Presents title review. Contact: Department of Pharmaceutical Chemistry, SSR College of Pharmacy, Silvassa, India.]

5. Tobias HJ, Zhang Y, Auchus RJ, Brenna JT. **Detection of synthetic testosterone use by novel comprehensive two-dimensional gas chromatography combustion-isotope ratio mass spectrometry.** Analytical Chemistry 2011;83(18):7158-7165. [Editor's Notes: Presents title study. Contact: Division of Nutritional Sciences, Cornell University, Ithaca, NY 14853, USA.]

* * * * * * * * * * * * * * * * * * * * * * * * *

THE JOURNAL/TEXTBOOK COLLECTION EXCHANGE

The Journal/Textbook Collection Exchange is a service intended to facilitate the transfer of unwanted journals and textbooks to forensic libraries or other *Microgram* subscribers.

The DEA Office of Forensic Sciences is looking for donation of the following items. If you can assist, please contact Dr. Bob Klein at: robert.x.klein –at– usdoj.gov (replace –at– with @)

1. *Journal of Forensic Sciences*, 1960 through 1965, either bound or individual issues.
2. *Journal of Forensic Sciences*, 1975, Issue #4.
3. *BDAC Bulletin*, Issues 2, 3, and 7 (these date from about 1968) – originals or good photocopies.
4. *BNDD Bulletin*, Issue 1 (April, 1969) – original or a good photocopy.

* * * * * * * * * * * * * * * * * * * * * * * * *

THE DEA FY 2012 STATE AND LOCAL FORENSIC CHEMISTS SEMINAR SCHEDULE

The FY 2012 schedule for the State and Local Forensic Chemists Seminar is as follows:

March 19-23, 2012
June 11-15, 2012
September 10-14, 2012

The school is open only to forensic chemists working for law enforcement agencies. It is intended for chemists who have completed their agency's internal training program and have also been working on the bench for at least one year. There is no tuition charge. The course is held at the Hyatt Place Dulles North Hotel in Sterling, Virginia (near the Washington/Dulles International Airport). A copy of the application form is reproduced on the last page of this issue of *Microgram Bulletin*. Completed applications should be mailed to the Special Testing and Research Laboratory at 22624 Dulles Summit Court, Dulles, VA 20166. For additional information, email DEA-Forensic Chemist Seminar -at- usdoj.gov (replace -at- with @).

* * * * * * * * * * * * * * * * * * * * * * * * *

SCIENTIFIC MEETINGS

Title: AAFS 64th Annual Scientific Meeting
Sponsoring Organization: American Academy of Forensic Sciences
Inclusive Dates: February 20-25, 2012
Location: Atlanta Marriott Marquis (Atlanta, GA)
Contact Information: See website
Website: www.aafs.org

DEA State and Local Forensic Chemist Seminar Application

Name: (PRINT NAME EXACTLY AS IT IS TO APPEAR ON CERTIFICATE)	Title:

Employer:

Your Office Mailing Address (include city, state, and zipcode):	Length of Service:

Business Telephone: ( ) -	Business Fax: ( ) -	Date of Application:

Email Address:

Education

College or University	Degree	Major

Please Check Which Techniques or Equipment Are Used in Your Laboratory

	Color Tests		UV
	Column Chromatography		IR
	Microcrystal Tests		CE
	Thin Layer Chromatography		GC/MS
	GC		Other (please specify)
	HPLC		Other (please specify)

Indicate Analytical Problem(s) Nominee Would Like to Have Covered:

Choice of Seminar Dates:
1st Choice: 2nd Choice:

Laboratory Chief/Director:

Printed Name:_____ Signature: _____

Title: _____ Date: _____

Phone: _____