U. S. Department of Justice
Drug Enforcement Administration
Diversion Control Division
8701 Morrissette Drive
Springfield, Virginia 22152-1080

www.dea.gov

October 27, 2017

The Honorable William H. Pryor, Jr.
Acting Chair
United States Sentencing Commission
One Columbus Circle, NE
Suite 2-500, South Lobby
Washington, DC 20002-8002

Dear Judge Pryor:

In August of 2017, the Commission published an issue for public comment on synthetic cathinones (such as methylone, MDPV, and mephedrone) and synthetic cannabinoids (such as JWH-018 and AM-2201), as well as tetrahydrocannabinol (THC). The Commission also sought comment regarding appropriate guideline amendments, including simplifying the process currently set forth in Application Note 6 to §2D1.1.[1] The Drug Enforcement Administration (DEA) is pleased to offer its perspective on these issues. Thank you in advance for considering our thoughts.

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Synthetic Cathinones
Issue 1

The Commission invites general comment on synthetic cathinones, particularly on their chemical structures, their pharmacological effects, potential for addiction and abuse, the patterns of abuse and harms associated with their abuse, and the patterns of trafficking and harms associated with their trafficking. How are synthetic cathinones manufactured, distributed, possessed, and used? What are the characteristics of the offenders involved in these various activities? What harms are posed by these activities? How do these harms differ from those associated with other controlled substances such as marihuana, cocaine, heroin, methamphetamine, or MDMA/Ecstasy?

As the DEA noted in its written testimony for the Commission's October 2017 hearing on Sentencing Policy for Synthetic Drugs, synthetic cathinones are generally manufactured in East Asia, predominantly in China. They are then distributed throughout Europe, North America, Australia, and other parts of the world.[2] Synthetic cathinones are created in laboratories and do not require any plant-based material. Producing synthetic cathinones requires relatively sophisticated scientific equipment, along with a relatively high degree of knowledge in chemistry. Synthetic cathinones are

1 U.S. SENTENCING COMM'N, FEDERAL REGISTER NOTICE OF AUGUST 2017 ISSUE FOR COMMENT, 82 Fed. Reg. 28382, https://www.ussc.gov/sites/default/files/pdf/amendment-process/federal-register-notices/20170824_fr_comment.pdf.
2 HEARING ON SENTENCING POLICY FOR SYNTHETIC DRUGS BEFORE U.S. SENTENCING COMM'N. (Oct. 4, 2017) (Statement of Neil Doherty), *available at* https://www.ussc.gov/policymaking/meetings-hearings/public-hearing-october-4-2017.

usually purchased in bulk, through mail order, online order, or in-person, through chemical brokers from China. DEA investigations reveal that the original supplier will often provide the package to a freight forwarding company or individual, who transfers it to another freight forwarder, who then takes custody and presents the package to customs for export. The combination of a chain of freight forwarders and multiple transfers of custody makes it difficult for law enforcement to track these packages.

Regarding the use of these substances, as the DEA has previously explained, these substances possess stimulant and/or hallucinogenic properties and the substitutions on the core structure impart these pharmacological effects to varying degrees.[3] Due to the similarity in chemical structures and sharing of some common mechanisms of actions with known stimulant drugs of abuse such as MDMA, methamphetamine, cocaine, and methcathinone, synthetic cathinones will share some similarities with these substances in regard to their abuse potential.[4] For further information, the DEA would direct the Commission to the statements made in the written documents previously provided to the Commission, as well as the oral testimony DEA provided at the public hearings on this topic.

Issue 2

The Commission invites general comment on whether and, if so, how the guidelines should be amended to account for synthetic cathinones. For example, should the Commission establish marihuana equivalencies for specific synthetic cathinones such as methylone, MDPV, and mephedrone? If so, what equivalencies should the Commission provide for methylone, MDPV, and mephedrone, and why? What factors should the Commission consider when deciding whether to account for these synthetic cathinones?

The DEA reaffirms the information and statements made in the written documents previously provided to the Commission, as well as the testimony it provided at the public hearings on this topic. The DEA continues to believe that a class approach for synthetic cathinones is viable and desirable. Indeed, there appeared to be a consensus on that point at the October 2017 public hearing. Please see the discussion of Issue 3 below for additional information.

Issue 3

As stated above, the Commission has received comment indicating that a large number of synthetic cathinones are currently available, and that new synthetic cathinones are regularly developed for illegal trafficking. Instead of providing marihuana equivalencies for individual synthetic cathinones, should the Commission consider establishing a single marihuana equivalency applicable to all synthetic cathinones? Are synthetic cathinones sufficiently similar to one another in chemical structure, pharmacological effects, potential for addiction and abuse, patterns of trafficking and abuse, and associated harms, to support the adoption of a broad class-based approach for sentencing purposes? If so, what marihuana equivalency should the Commission provide for synthetic cathinones as a class and why? What factors should the Commission account

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3 *See* HEARING ON SENTENCING POLICY FOR SYNTHETIC DRUGS BEFORE U.S. SENTENCING COMM'N. (Oct. 4, 2017) (Statement of Terrence Boos & Cassandra Prioleau), *available at* https://www.ussc.gov/policymaking/meetings-hearings/public-hearing-october-4-2017.

4 M.B. Gatch, M.A. Rutledge & M.J. Forster, *Discriminative and Locomotor Effects of Five Synthetic Cathinones in Rats and Mice*, 232 Psychopharmacology, 1197-1205 (2015).

for if it considers adopting a broad class-based approach for synthetic cathinones? Should the Commission define "synthetic cathinones" for purposes of this broad class-based approach? If so, how? Are there any synthetic cathinones that should not be included as part of a broad class-based approach and for which the Commission should provide a marihuana equivalency separate from other synthetic cathinones? If so, what equivalency should the Commission provide for each such synthetic cathinone, and why?

What are the advantages and disadvantages of a broad class-based approach for synthetic cathinones? If the Commission were to provide a different approach to account for synthetic cathinones in the guidelines, what should that different approach be?

As the DEA has previously explained, the process currently set forth in Application Note 6 to §2D1.1 for addressing synthetic drugs is cumbersome and inefficient. The DEA, therefore, suggests that the Commission adopt a class approach that would treat a new synthetic drug the same as other substances in the same drug class. This approach will result in sentences that are more predictable, consistent, and fair.[5] Such an approach will also conserve scarce judicial resources and promote efficiency by eliminating the "battle of the experts" that frequently occurs under the current version of Application Note 6.

In its written statement and oral testimony at the October 4, 2017 hearing on Sentencing Policy and Synthetic Drugs, the DEA specifically addressed whether synthetic cathinones are sufficiently similar to one another in chemical structure, pharmacological effects, potential for addiction and abuse, patterns of trafficking and abuse, and associated harms, to support the adoption of a class-based approach for sentencing purposes.[6] As the DEA explained in its written statement and during its oral testimony at the hearing, the cathinone structural class is well established and accepted in the scientific literature. The DEA's prior statements and testimony also addressed the pharmacological effects of synthetic cathinones, as well as the difficulties in determining potency for these ever-evolving drugs.

Synthetic cathinones are highly toxic, and the adverse health effects include significant sympathomimetic effects, as well as psychosis, agitation, aggression, and sometimes violent and bizarre behaviors such as episodes of delirium with persecution.[7] Deaths have been directly connected to synthetic cathinone consumption.[8] Even when death does not result, emergency room physicians testifying at the hearing in October described patients suffering very serious and life

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5 Kenneth A. Blanco, Acting Assistant Attorney General & Zachary C. Bolitho, Counsel to the Deputy Attorney General, Dep't of Justice, Annual Letter to William H. Pryor, Jr., Acting Chair, U.S. SENTENCING COMM'N (July 31, 2017).

6 *See* HEARING ON SENTENCING POLICY FOR SYNTHETIC DRUGS BEFORE U.S. SENTENCING COMM'N. (Oct. 4, 2017) (Statement of Terrence Boos & Cassandra Prioleau), *available at* https://www.ussc.gov/policymaking/meetings-hearings/public-hearing-october-4-2017.

7 *Id.*

8 K. Kobacs, A.R. Toth & E.M. Kereszty, *A New Designer Drug: Methylone Related Death*, 153 Orv Hetil,271-276 (2012); B.L. Murray, C.M. Murphy & M.C. Beuhler, *Death Following Recreational Use of Designer Drug "Bath Salts" Containing 3,4-methylenedioxypyrovalerone (MDPV)*, 8 Journal of Medical Toxicology,69–75 (2012); D.M. Wood, S. Davies, S.L. Greene, J. Button, D.W. Holt, J. Ramsey & P.I. Dargan, *Case Series of Individuals with Analytically Confirmed Acute Mephedrone Toxicity*, 48 Clinical Toxicology, 924–927 (2010); L.J. Marinetti & H.M. Antonides, *Analysis of Synthetic Cathinones Commonly Found in Bath Salts in Human Performance and Postmortem Toxicology: Method Development, Drug Distribution and Interpretation of Results*, 37 Journal of Analytical Toxicology, 135-146 (2013).

threatening harms as a result of the consumption of synthetic cathinones.[9] In addition to the chemical structure and pharmacological effects, when determining the marijuana equivalency for the entire class of synthetic cathinones, the Commission should consider the unpredictable toxicity and medical risks associated with the use of the growing number of synthetic cathinone concoctions. The Commission should also consider the fact that these new substances are being designed to evade our drug laws.

As the Commission is considering a particular marijuana equivalency for the class of synthetic cathinones, the DEA would encourage the Commission to consider the 1:500 ratio that currently exists for MDMA, as well as the 1:380 ratio that currently exists for methcathinone. The DEA would further request that the Commission carefully consider the conclusions that have been reached by the courts when applying the Application Note 6 process in synthetic cathinone cases. Although the courts have not been entirely uniform in their treatment of synthetic cathinones, they have generally used (aside from methylone)[10] either the 1:500 ratio for MDMA or the 1:380 ratio for methcathinone.[11]

Synthetic Cannabinoids
Issue 1

The Commission invites general comment on organic and synthetic tetrahydrocannabinol (THC), particularly on its chemical structure, its pharmacological effects, potential for addiction and abuse, the patterns of abuse and harms associated with its abuse, and the patterns of trafficking and harms associated with its trafficking. How is THC manufactured, distributed, possessed, and used? What are the characteristics of the offenders involved in these various activities? What harms are posed by these activities? How do these harms differ from those associated with other controlled substances such as marihuana, cocaine, heroin, or methamphetamine?

The Commission further seeks comment on whether, and if so how, the Commission should

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9 "Neurologically, users may present with tremors, rigidity, and seizures… All organ systems can be affected, with muscle breakdown, liver damage, kidney failure, and myocardial injury all being reported and experienced personally in our program. Deaths have been widely reported with synthetic cathinone use in the U.S. and Europe from both direct and indirect toxicity, such as suicide." HEARING ON SENTENCING POLICY FOR SYNTHETIC DRUGS BEFORE U.S. SENTENCING COMM'N. (Oct. 4, 2017) (Statement of Christopher P. Holstege, Chief, Division of Medical Toxicology, and Heather A. Borek, M.D., Assistant Professor of Emergency Medicine, University of Virginia School of Medicine), https://www.ussc.gov/sites/default/files/pdf/amendment-process/public-hearings-and-meetings/20171004/Borek-Holstege.pdf.

10 In the context of methylone, some courts have used a 1:500 ratio, while others have used a 1:250 ratio. *Compare United States v. McClure*, 694 F. App'x 284 (5th Cir. 2017) (affirming, on plain error review, the district court's adoption of 1:500 ratio for methylone), *with United States v. Marte*, 586 F. App'x 574, 575 (11th Cir. 2014) (noting that the district court reasonably used 1:250 ratio for methylone); *see also United States v. Malespin*, Case No. 1:15-CR-20350 (S.D. Fla. Oct. 27, 2015) (Doc. 62 at pg. 30) (adopting ratio of 1:250 for methylone).

11 *See, e.g.*, *United States v. Brey*, 627 F. App'x 775, 780-81 (11th Cir. 2015) (affirming the district court's use of 1:500 ratio for ethylone); *United States v. Lane*, 616 F. App'x 328, 329 (9th Cir. 2015) (affirming the district court's use of methcathinone (1:380 ratio) for MDVP, a-PVP, and a-PBP); *United States v. Holmes*, 2016 WL 1611579, at *8 (D. Haw. Apr. 22, 2016) (finding that 1:380 ratio was appropriate for ethylone); *United States v. Moreno*, 2015 WL 6071680, at *5 (W.D. Wisc. Oct. 15, 2015) (using the 1:380 methcathinone equivalency for Alpha-PVP); *United States v. Emerson*, 2016 WL 1047006, at *5 (D. Vt. Mar. 10, 2016) (same).

change how the guidelines account for THC. As stated above, the marihuana equivalencies of both types of THC, organic and synthetic, have the same ratio—1 gm of THC = 167 gm of marihuana. Is the 1:167 ratio in marihuana equivalency for both types of THC appropriate? Should the Commission establish a different ratio for both types of THC? If so, what ratio should the Commission establish and why? Should THC (organic) and THC (synthetic) have the same ratio in marihuana equivalency? Should the Commission instead establish one ratio for THC (organic) and a different ratio for THC (synthetic)? If so, what ratio should the Commission establish for each substance and why?

Chemically, tetrahydrocannabinol is known as (6aR-trans)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3 -pentyl-6*H*-dibenzo-[b,d]pyran-1-ol or (-)Δ9-(trans)-tetrahydrocannabinol. It is an optically active resinous substance, extremely lipid soluble, and insoluble in water. Tetrahydrocannabinol is commonly referred to as Δ9-THC or THC. The chemical structure remains the same regardless of the source (i.e. extracted from marijuana or synthesized in a laboratory).

THC is the primary psychoactive component of marijuana. Pharmacological effects of THC are thought to be mediated through at least two distinct receptors designated as CB1 and CB2. THC has been shown to have a similar binding affinity for both cannabinoid receptors, while acting as a partial agonist at these receptors. Research has shown that CB1 receptors are found predominantly in the brain and the binding of a substance, like THC, to the CB1 receptor and subsequent activation of the CB1 receptor, lead to the psychoactive effects commonly observed following the ingestion of marijuana.

Both preclinical and clinical studies have demonstrated that THC possesses the attributes associated with drugs of abuse. THC is an effective reinforcer in laboratory animals, including primates and rodents. These animal studies predict and support the observations that THC, whether smoked as marijuana or administered by other routes, produces reinforcing effects in humans. Such reinforcing effects can account for repeated use and ultimately abuse.

THC can be obtained from two different sources: as a substance produced within the marijuana plant (organic) or produced synthetically, such as in a laboratory or pharmaceutical company. Regardless of the source, organic and synthetic THC have the same chemical structure and pharmacological effects.

The DEA would note that the U.S. Food and Drug Administration (FDA) has approved two drug products containing synthetic THC and another product containing nabilone, a synthetic substance that is structurally and pharmacologically related to THC. Marinol (also referred to as dronabinol), a Schedule III product containing synthetic THC formulated in sesame oil in soft gelatin capsules, is indicated to counteract the nausea and vomiting associated with chemotherapy. It is also known to stimulate appetite in AIDS patients affected by wasting syndrome. In July 2016, the FDA approved Syndros®, an oral formulation of dronabinol, for the treatment of patients experiencing chemotherapy-induced nausea and vomiting who have not responded to conventional antiemetic therapies, as well as for treating anorexia associated with weight loss in patients with AIDS. The DEA has published an interim final rule[12] controlling Syndros® as a Schedule II product under the

12 Rules and Regulations, Fed. 82 Reg. 55 (March 23, 2017) (Docket No. DEA–344)

CSA. Cesamet®, a drug product containing the Schedule II substance nabilone, a synthetic substance structurally and pharmacologically related to THC, is indicated for the treatment of nausea and vomiting associated with cancer chemotherapy. Besides the cannabinoid-containing drug products approved by the FDA, all other naturally occurring cannabinoids and their derivatives (from cannabis) and their synthetic equivalents with similar chemical structure and pharmacological activity are included in the CSA as Schedule I substances.

In terms of pharmacological effects, THC produces euphoria, disinhibition, amnesia, anxiety/nervousness, ataxia, confusion, dizziness, hallucination, paranoid reaction, somnolence, nausea, vomiting, tachycardia, acute and chronic respiratory effects, and immunosuppression, as well as behavioral and cognitive impairment.[13,14] Dose dependent relationships between THC exposure and both tachycardia and hypertension have been reported. In a 2012 study, administration of oral THC to healthy individuals was associated with behavioral and physiological effects that include anxiety, dysphoria, positive psychotic symptoms, physical and mental sedation, subjective intoxication, and an increase in heart rate.[15] In another clinical study, the negative health effects associated with pure THC was demonstrated following its administration to healthy individuals under controlled conditions.[16] In this study, cannabidiol (CBD, a cannabinoid found with the marijuana plant) or placebo was administered ahead of intravenous THC to determine if CBD inhibited THC-elicited psychosis and cognitive impairment. The results demonstrated that subjects receiving CBD prior to THC exhibited less THC-paranoia and better episodic memory as compared to subjects receiving THC alone. The authors stated that these findings supported the idea that high-THC/low-CBD containing cannabis products are associated with increased risks for mental health problems. DEA sees no reason to make any changes to the guidelines treatment of THC at this time.

Issue 2

The Commission invites general comment on synthetic cannabinoids, particularly on their chemical structures, their pharmacological effects, potential for addiction and abuse, the patterns of abuse and harms associated with their abuse, and the patterns of trafficking and harms associated with their trafficking. How are synthetic cannabinoids manufactured, distributed, possessed, and used? What are the characteristics of the offenders involved in these various activities? What harms are posed by these activities? How do these harms differ from those associated with other controlled substances such as marihuana, cocaine, heroin, or methamphetamine?

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13 Proposed Rules, Fed. 81 Reg. 156 (August 12, 2016) (Docket No. DEA–427)
14 Marinol (Dronabinol) NDA 18-651/S-021, Unimed Pharmaceuticals, Inc., www.fda.gov/ohrms/dockets/dockets/05n0479/05N-0479-emc0004-04.pdf (2004)
15 R. Martin-Santos, J.A. Crippa, A. Batalla, S. Bhattacharyya, Z. Atakan, S. Borgwardt, P. Allen, M. Seal, K. Langohr, M. Farre, AW. Zuardi & P.K. McGuire, *Acute Effects of a Single, Oral Dose of d9-tetrahydrocannabinol (THC) and Cannabidiol (CBD) Administration in Healthy Volunteers*, 18 Current Pharmaceutical Design, 4966-79 (2012)
16 A. Englund, P.D. Morrison, J. Nottage, D. Hague, F. Kane, S. Bonaccorso, J.M. Stone, A. Reichenberg, R. Brenneisen, D. Holt, A. Feilding, L. Walker, R.M. Murray & S. Kapur, *Cannabidiol Inhibits THC-elicited Paranoid Symptoms and Hippocampal-dependent Memory Impairment*, 27 Journal of Psychopharmacology, 19-27 (2013).

Chemistry and general synthesis

Compared to THC, synthetic cannabinoids represent a structurally diverse group of substances that retain activity at the CB1 receptor. These substances have been synthesized in laboratories and have been the subject of many structure activity relationships where the core structure serves as a skeleton. A variety of substitutions have been made to the core structure to investigate changes in activity that are well documented in the scientific and patent literature. The synthetic cannabinoids that have been observed on the illicit market can be synthesized in just a few chemical reactions. By starting with a common core structure, a host of synthetic cannabinoids can be introduced into the illicit market by simply changing one of the reactants in the synthetic sequence.

Pharmacological Effects

The synthetic cannabinoids encountered on the illicit market are predominantly potent cannabinoid agonists that are pharmacologically similar to THC. Synthetic cannabinoids, like THC, bind to and activate the CB1 receptor, while producing euphoric and hallucinogenic effects. While no human studies have been conducted regarding these illicit synthetic cannabinoids, many case reports have documented the unintended consequences following the use of these toxic chemicals.[17,18,19,20] Serious bodily harm and adverse effects have occurred from the ingestion of synthetic cannabinoids that have included seizures, cardiotoxicity, psychosis, agitation, multi-organ failure, central nervous system deficits and death amongst many others.

Potential for Addiction and Abuse

Since the first United States encounter of synthetic cannabinoids in November 2008 by Customs and Border Protection, the number of substances encountered in the illicit market place has steadily increased. Based on law enforcement seizures, case reports, hospital admissions and medical examiner data, the use of synthetic cannabinoids has shifted from the potential for being addictive and abused, to the realization that these drugs are causing irrefutable harm to the users, their families and the communities surrounding them. The imminent threat to public safety has led the DEA to temporarily schedule 22 synthetic cannabinoids to date. And, Congress passed legislation in 2012 controlling 15 additional synthetic cannabinoids.[21] The abuse potential of synthetic cannabinoids is associated with their ability to evoke cannabinoid-like subjective effects similar to those evoked by THC, a Schedule I cannabinoid substance. The American Association of Poison Control Centers

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17 M.D. Schwartz, J. Trecki, L.A. Edison, A.R. Steck, J.K. Arnold & R.R. Gerona, *A Common Source Outbreak of Severe Delirium Associated with Exposure to the Novel Synthetic Cannabinoid ADB-PINACA*, 48 Journal of Emergency Medicine,573-80 (2015).

18 J. Trecki, R.R. Gerona & M.D. Schwartz, *Synthetic cannabinoid-related illnesses and deaths*, 373 New England Journal of Medicine, 103-107 (2015).

19 J.A. Tyndall, R. Gerona, G. De Portu, J. Trecki, J. Lucas, J. Slish, K. Rand, L. Bazydlo, M. Holder, M.F. Ryan, P. Myers, N. Iovine, M. Plourde, E. Weeks, J.R. Hanley, G. Endres, D. St Germaine, P.J. Dobrowolski & M. Schwartz, *An Outbreak of Acute Delirium from Exposure to the Synthetic Cannabinoid AB-CHMINACA*, 53 Clin Toxicol (Phila), 950-6, (2015).

20 A.J. Adams, S.D. Banister, L. Irizarry, J. Trecki, M. Schwartz & R. Gerona, *"Zombie" Outbreak Caused by the Synthetic Cannabinoid AMB-FUBINACA in New York*, 376 New England Journal of Medicine, 235-242 (2017).

21Section 1152 of Food and Drug Administration Safety and Innovation Act (FDASIA), Pub. L. 112-144, July 9, 2012

continues to publish data from thousands of calls each year regarding adverse effects experienced following the abuse of synthetic cannabinoids containing products.[22]

Patterns of abuse and harms associated with their abuse

The popularity of synthetic cannabinoids and their associated products has increased since January 2010, as evidenced by the increasing number of law enforcement seizures and public health and media reports. The Department of Health and Human Services, along with a recent study, have observed that synthetic cannabinoid abuse has been repeatedly noted in athletes, military personnel, employees who undergo frequent drug testing, and other individuals seeking intoxication while hoping to evade detection.[23] These substances and their products, commonly marketed as "legal highs" with a disclaimer of "not for human consumption," are routinely sold through venues including the internet or darkweb marketplaces, gas stations, convenience and corner stores. Recent data originating from a multi-state outbreak involving synthetic cannabinoids demonstrated that while the predominant users of these products are between the ages of 18-34, users under the age of 12 years old and those up to and older than 65 are also abusing synthetic cannabinoid products.[24,25] A person with a smartphone and a form of currency can easily locate and purchase any number of various synthetic cannabinoids containing products discretely. Aside from the toxicity and bodily harm previously described, emergency responders are at a disadvantage because (given the proliferation of different synthetic cannabinoids) they often do not know what actual substance was ingested by the patient. And, the synthetic cannabinoids often do not appear on regular drug screens. Further compounding the problem is that adverse effects routinely render a patient either unconscious or in an agitated, psychotic and/or disoriented state so severe that the user is unable to communicate to a first responder what product was used. Additional information regarding the adverse health impacts of synthetic cannabinoids can be found in a statement the DEA provided to the Commission on March 15, 2017.[26]

Patterns of trafficking and harms associated with their trafficking

Synthetic cannabinoids are predominantly produced in Chinese laboratories. They are then shipped in powder form through freight forwarding companies before ending up in the United States. The powder is then commonly dissolved in a liquid and applied to leafy plant material that resembles marijuana. The finished product is packaged in multiple forms that can include rolling into cigarettes or joints, sold in non-descript plastic baggies, or most commonly inserted into a foil packaging, adorned with colorful cartoon characters or other pictures that attempt to distinguish brand and seller identity. They are often sold using names such as "Spice" and "K2." These various

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22 American Association of Poison Control Centers, "Synthetic Cannabinoids," http://www.aapcc.org/alerts/synthetic-cannabinoids/ (reporting 1,497 exposures from January 1, 2017 to September 2017, and reporting that in 2015 there were 7,794 reported exposures).

23 E.E. Bonar, L. Ashrafioun & M.A. Ilgen, *Synthetic Cannabinoid Use Among Patients in Residential Substance Use Disorder Treatment: Prevalence, Motives, and Correlates*, 143 Drug and Alcohol Dependence, 268-71 (2014).

24 J. Trecki, R.R. Gerona & M.D. Schwartz, *Synthetic cannabinoid-related illnesses and deaths*, 373 New England Journal of Medicine, 103-107 (2015).

25 MMWR Morbidity Mortality Weekly Report, 64(39), 1121-2 (2015).

26 Statement of Dr. Terry Boos & Shontal Linder, Hearing on Sentencing Policy for Synthetic Drugs at 23-24 (March 15, 2017) (https://www.ussc.gov/sites/default/files/pdf/amendment-process/public-hearings-and-meetings/20170418/DEA.pdf).

products are then distributed to retail outlets or can be sold directly to users through various mail services via internet websites. The number of synthetic cannabinoids present in the United States has increased dramatically in recent years. For example, according to the DEA National Forensic Laboratory Information System (NFLIS), law enforcement encounters of substances identified as synthetic cannabinoids by federal, state, and local forensic laboratories increased from 23 reports in 2009 to 37,500 reports in 2014.[27] As of October 27, 2017, NFLIS has identified 191,219 reports of synthetic cannabinoids.

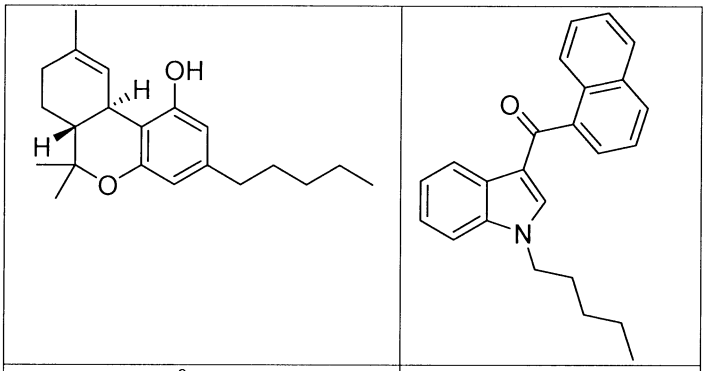
Issue 3

As noted above, courts frequently identify tetrahydrocannabinol (THC) as the most closely related controlled substance referenced in the guidelines in cases involving synthetic cannabinoids. Under the current guidelines, including Application Note 6 to §2D1.1, is this determination appropriate? Is organic and synthetic THC the most closely related controlled substance to (1) JWH-018, (2) AM-2201, and (3) synthetic cannabinoids in general? If not, is there any controlled substance referenced in §2D1.1 that is most closely related to synthetic cannabinoids? If so, what substance?

The Commission further seeks comment on whether and, if so, how the guidelines should be amended to account for synthetic cannabinoids. For example, should the Commission establish marihuana equivalencies for specific synthetic cannabinoids such as JWH-018 and AM-2201? If so, what equivalencies should the Commission provide for JWH-018 and AM-2201, and why? What factors should the Commission consider when deciding whether to account for these synthetic cannabinoids?

Synthetic cannabinoids are by definition man-made chemicals. Each substance identified in the illicit marketplace represents a different drug that, in almost all cases, has never been found in nature. Rather, it was invented and manufactured within a laboratory setting. Synthetic cannabinoids are much more harmful than THC. Nevertheless, under the current guidelines, the most substantially similar controlled substance listed is THC. That is true based on the following factors: 1) THC, like a synthetic cannabinoid that would be compared to it, is a single chemical; 2) the pharmacological effects of THC are substantially similar to the synthetic cannabinoid compared to it; and 3) the relative potency of the synthetic cannabinoid in most cases is equal to or greater than that of THC. Using the current guidelines, THC, despite its chemical structural differences compared to synthetic cannabinoids, would be the most closely related substance when comparing substances, including JWH-018, AM2201, and synthetic cannabinoids in general.

27 Statement of Chuck Rosenberg, Acting DEA Administrator before the Senate Judiciary Committee at 2 (June 7, 2016) (https://www.judiciary.senate.gov/imo/media/doc/06-07-16%20Rosenberg%20Testimony.pdf).



Δ^9-THC	JWH-018

DEA has encountered and identified many synthetic cannabinoids currently available in the illicit marketplace. In addition, the law enforcement and scientific community together has observed that many synthetic cannabinoids are either taken directly or derived from publically available patent literature and/or scientific publications. It is possible that hundreds if not thousands of new synthetic cannabinoids could be created based on this literature. As a result, the DEA does not recommend specific marijuana equivalencies for each synthetic cannabinoid. Rather, the DEA would prefer a class approach. Such an approach would ensure that the currently available synthetic cannabinoids and future variations are captured within the sentencing guidelines.

Synthetic cannabinoids continue to demonstrate serious adverse effects across age brackets that greatly surpass those observed with THC, are frequently marketed to and abused by those of a young age, repeatedly demonstrate a threat to public safety, continue to be illegally imported into the United States, and are diluted to produce a large number of doses per gram.

Issue 4

As stated above, the Commission has received comment indicating that a large number of synthetic cannabinoids are currently available, and that new synthetic cannabinoids are regularly developed for illegal trafficking. Instead of providing marihuana equivalencies for individual synthetic cannabinoids, should the Commission consider establishing a single marihuana equivalency applicable to all synthetic cannabinoids? Are synthetic cannabinoids sufficiently similar to one another in chemical structure, pharmacological effects, potential for addiction and abuse, patterns of trafficking and abuse, and associated harms, to support the adoption of a broad class-based approach for sentencing purposes? If so, what marihuana equivalency should the Commission provide for synthetic cannabinoids as a class and why? What factors should the Commission account for if it considers adopting a broad class-based approach for synthetic cannabinoids? Should the Commission define "synthetic cannabinoids" for purposes of this broad class-based approach? If so, how? Are there any synthetic cannabinoids that should not be included as part of a broad class-based approach and for which the Commission should provide a marihuana equivalency separate from other synthetic cannabinoids? If so, what equivalency should the Commission provide for each such synthetic cannabinoid, and why?

What are the advantages and disadvantages of a broad class-based approach for synthetic cannabinoids? If the Commission were to provide a different approach to account for synthetic cannabinoids in the guidelines, what should that different approach be?

To date, synthetic cannabinoids encountered in the illicit market have been from several chemical structural classes including, but not limited to, 1,3-disubstituted indoles, 1,3-disubstituted indazoles, and cyclohexylphenols. However, in light of the market dynamics that have been observed thus far in response to legislative and regulatory drug control actions, it is expected that synthetic cannabinoids with new structural backbones will enter the illicit market. As observed with other synthetic drug classes, manufacturers of synthetic cannabinoids routinely make small modifications to the chemical structure with the intention to retain the pharmacological activity for the user. Defining a limited number of structural classes would be circumvented by manufacturers attempting to avoid prosecution and ultimately sentencing. We suggest that the Commission consider establishing a single marihuana equivalency applicable to all synthetic cannabinoids.

Currently, the term "synthetic cannabinoids" represents a group of substances with a common pharmacological property: activation of the CB1 cannabinoid receptor. DEA recommends defining a "synthetic cannabinoid" as a substance that acts as an agonist at the CB1 receptor.

Regarding potency, drug discrimination data are available on at least 26 different synthetic cannabinoids. JWH-018 was shown in the drug discrimination assay to be approximately 3 times as potent as THC, while AM2201 was shown to be approximately 5 times as potent as THC using the same assay.[28] Newer synthetic cannabinoids have been shown to be even more potent than either JWH-018 or AM2201.[29,30] On rare occasions, synthetic cannabinoids have been shown to be less potent in the drug discrimination assay than THC. We have observed that substances with a lower potency are often abandoned by manufactures following negative user reports relating to their pharmacological effects.[31] And, just as with cathinones, because potency compares the amounts of drugs that produce the same or similar effect, users can simply adjust the dose of a given drug to achieve the desired effects. Therefore, it is not advisable to use the pharmacological potency of the drug as the sole factor in determining the marijuana equivalency. Other factors such as toxicity, adverse impacts on public health and risks of adverse impacts on public health, should also be considered. Again, as in the case of cathinones, the equivalency for the class of cannabinoids should reflect the fact that all of the substances in the class were, and will be, created to skirt our legal system.

As previously explained with regard to synthetic cathinones, the advantage to a class approach for synthetic cannabinoids would be to offer clarity and consistency and promote judicial economy.

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28 MB Gatch and MJ Forster, *Δ9-Tetrahydrocannabinol-like discriminative stimulus effects of compounds commonly found in K2/Spice*, 25(8) Behavioural Pharmacology, 750-757 (2014).
29 MB Gatch and MJ Forster, *Δ9-Tetrahydrocannabinol-like effects of novel synthetic cannabinoids found on the gray market*, 26(5) Behavioural Pharmacology, 460-468 (2015).
30 MB Gatch and MJ Forster, *Δ9-Tetrahydrocannabinol-like effects of novel synthetic cannabinoids in mice and rats*, 233 Psychopharmacology, 0901-1910 (2016).
31 J.L. Wiley, J.A. Marusich, T.W. Lefever, K.R. Antonazzo, M.T. Wallgren, R.A. Cortes, P.R. Patel, M. Grabenauer, K.N. Moore & B.F. Thomas, *AB-CHMINACA, AB-PINACA, and FUBIMINA: Affinity and Potency of Novel Synthetic Cannabinoids in Producing Δ9-Tetrahydrocannabinol-Like Effects in Mice*, 354 Journal of Pharmacology and Experimental Therapeutics, 328-39 (2015).

Creating an equivalency for the class would also provide defendants with notice of the sentence they face, and it would serve to simplify the guidelines.

Issue 5

If the Commission was to establish a single marihuana equivalency applicable to all synthetic cannabinoids as a class, should this class-based equivalency also apply to synthetic tetrahydrocannabinol (THC)? Is synthetic THC sufficiently similar to other synthetic cannabinoids in chemical structure, pharmacological effects, potential for addiction and abuse, patterns of trafficking and abuse, and associated harms, to be included as part of a broad class-based approach for synthetic cannabinoids? Should the Commission instead continue to provide a marihuana equivalency for synthetic THC separate from other synthetic cannabinoids?

The DEA recommends that the Commission establish a class approach for all synthetic cannabinoid substances not currently referenced in the guidelines. THC is already listed in the guidelines, already has a marijuana equivalency, and the DEA sees no reason to make any changes to the guidelines treatment of THC at this time.

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The DEA appreciates the opportunity to provide the Commission with its views, comments, and suggestions. As always, the DEA looks forward to working with the Commission during the remainder of the amendment cycle.

Sincerely,

Neil Doherty
Deputy Assistant Administrator
Diversion Control Division

cc: Commissioners
Ken Cohen, Staff Director
Kathleen Grilli, General Counsel