U.S. Department of Justice

Drug Enforcement Administration

Schedules of Controlled Substances: Placement of quinolin-8-yl 1-pentyl-1*H*-indole-3-carboxylate (PB-22; QUPIC), quinolin-8-yl 1-(5-fluoropentyl)-1*H*-indole-3-carboxylate (5-fluoro-PB-22; 5F-PB-22), *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide (AB-FUBINACA) and *N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide (ADB-PINACA) into Schedule I

Background, Data, and Analysis:
Eight Factors Determinative of Control and Findings Pursuant to 21 U.S.C. 812(b)

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I. Background

On February 10, 2014, the Deputy Administrator of the Drug Enforcement Administration (DEA) published a Final Order in the Federal Register (79 FR 7577) temporarily placing four substances in schedule I of the Controlled Substances Act (CSA) upon finding that these synthetic cannabinoid (SC) substances posed an imminent threat to public safety. The four SCs temporarily controlled under the CSA are quinolin-8-yl 1-pentyl-1*H*-indole-3-carboxylate (PB-22; QUPIC), quinolin-8-yl 1-(5-fluoropentyl)-1*H*-indole-3-carboxylate (5-fluoro-PB-22; 5F-PB-22), *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide (AB-FUBINACA), and *N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide (ADB-PINACA). That Final Order, which became effective on the date of publication, was based on findings by the Deputy Administrator of the DEA that the temporary scheduling of these four SCs was necessary to avoid an imminent hazard to the public safety pursuant to 21 U.S.C. 811(h)(1). These four SCs have not been investigated for medical use nor are they intended for human use. With no known legitimate use and safety information, manufacturers are surreptitiously adulterating plant material with these SCs and distributors are selling the associated products which pose potentially dangerous consequences to the consumer. The adulterated products are marketed under various brand names (e.g., Sunburst, Joker Chronic Hypnotic, Dr. Feelgood, Cloud Nine, Bam Bam, Mind Trip, OMG, Crazy Clown, Black Mamba, Scooby Snax, Maui Maui, Bizarro) and sold under the guise of herbal incense products and as legal alternatives to marijuana.

Data from law enforcement, health care practitioners, and scientific and medical literature indicate that these products are being abused for their psychoactive properties in the absence of information regarding their safety. There have been reports of admissions to hospital emergency departments (ED) following abuse of these synthetic cannabinoids.

As described in the February 10, 2014 Final Order, PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA are SCs that are pharmacologically similar to delta-9-tetrahydrocannabinol (THC), and schedule I SCs such as JWH-018 and AM2201. The Assistant Secretary of Health for the U.S. Department of Health and Human Services (HHS) has advised that there are no exemptions or approvals in effect for PB-22, 5F-PB-22, AB-FUBINACA, or ADB-PINACA under section 505 (21 U.S.C. 355) of the Federal

Food, Drug, and Cosmetic Act. As stated by the HHS, PB-22, 5F-PB-22, AB-FUBINACA and ADB-PINACA have no known accepted medical use. They are not the subject of any approved new drug applications (NDAs) or investigational new drug applications (INDs), and are not currently marketed as approved drug products.

The Food and Drug Administration (FDA) recommends that 1-pentyl-1*H*-indole-3-carboxylic acid 8-quinolinyl ester or quinolin-8-yl 1-pentyl-1*H*-indole-3-carboxylate, also known as PB-22; quinolin-8-yl 1-(5-fluoropentyl)-1H-indole-3-carboxylate, also known as 5F-PB-22; *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide, also known as AB-FUBINACA; and *N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide, also known as ADB-PINACA, and their salts, be placed into schedule I of the Controlled Substances Act (CSA).

II. Eight Factors Determinative of Control

In accordance with the provisions of 21 U.S.C. 811(b) of the Controlled Substances Act (CSA), the DEA has gathered the necessary data, including scientific, public health, and law enforcement information on these four substances, as well as their associated products. The DEA collected data in light of the information to be considered under 21 U.S.C. 811(c). On December 30, 2014, the DEA requested a scientific and medical evaluation and scheduling recommendation from the Assistant Secretary of Health for HHS for PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA pursuant to 21 U.S.C. 811(b). Administrative responsibilities for evaluating a substance for control under the CSA are performed for the HHS by the FDA, with the concurrence of the National Institute on Drug Abuse (NIDA) ((Memorandum of Understanding, 50 FR 9518–20) (Mar. 8, 1985)). Upon receipt and evaluation of the scientific and medical evaluations and scheduling recommendations from the Assistant Secretary, the DEA reviewed these documents and all other relevant data and conducted its own eight-factor analysis on these SCs pursuant to 21 U.S.C. 811(c). The DEA's eight-factor review as presented below finds that PB-22, 5F-PB-22, AB-FUBINACA,ADB-PINACA, and their salts warrant control in schedule I of the CSA.

Factor 1: The Actual or Relative Potential for Abuse

In addition to the information the HHS provided in its scientific and medical evaluation document for PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA (HHS review, 2015a,b,c,d), the DEA considers all other relevant data regarding the actual or relative potential for abuse. The first factor the DEA must consider is the actual or relative potential for abuse of PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA. The term "abuse" is not defined in the CSA. However, the legislative history of the CSA suggests that the DEA consider the following criteria in determining whether a particular drug or substance has a potential for abuse[1]:

a) *There is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or of the community; or*

b) *There is significant diversion of the drug or drugs containing such a substance from legitimate drug channels; or*

c) *Individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice; or*

d) *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.*

a. There is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.

[1] Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970); reprinted in 1970 U.S.C.C.A.N. 4566, 4603.

Review of scientific and medical literature indicates that the ingestion of synthetic cannabinoids leads to adverse health effects. Specifically, adverse effects following ingestion have included: seizures, neurotoxicity, and death for PB-22 (Guglemann et al., 2014; Gerostamoulos et al., 2015); respiratory failure, organ failure, and death for 5F-PB-22 (Behonick et al., 2014; Santacroce et al., 2015; Trecki et al., 2015); diaphoresis, nausea, confusion, tachycardia, and death for AB-FUBINACA (Trecki et al., 2015; local law enforcement data); and anxiety, delirium, psychosis, aggression, and seizures for ADB-PINACA (Monte et al., 2014; Schwartz et al., 2015; Trecki et al., 2015).

The American Association of Poison Control Centers[2] (AAPCC) reported 7,779 exposures to SCs from January 1 through December 31, 2015. The significance of this value is based upon reporting of human exposures to SCs since 2011. While 2012 – 2014 saw a reduction in exposure calls to AAPCC, 2015 records demonstrate resurgence in calls to poison centers regarding SCs. In addition, the largest monthly tally ever recorded by AAPCC in reference to SCs occurred in April 2015, with 1,511 calls.

b. There is significant diversion of the drug or substance from legitimate drug channels

The HHS stated that there are no FDA-approved drug products containing PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA in the United States and there appear to be no legitimate sources for these substances as marketed drugs. Therefore this criterion for assessing abuse potential of these SCs is not applicable.

[2] The American Association of Poison Control Centers collects information logged by the numerous regional Poison Control Centers (PCCs). Records are from self-reported calls; therefore, they reflect only information provided when the public or healthcare professional reports an actual or potential exposure to a substance (e.g. an ingestion, inhalation, or topical exposure), or requests informational material. It warrants noting that these exposures do not inherently represent an instance of poisoning or overdose. The AAPCC is not able to completely verify the accuracy of every report made to member centers. Additional exposures may go unreported to PCs and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance. The AAPCC indicated that a significant proportion of the reports were generated from hospital emergency departments or en-route to a medical treatment facility.

c. *Individuals are taking the substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice*

According to the HHS, because PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA are not approved for medical use and are not formulated or available for clinical use, the human use of these substances is assumed to be on an individual's own initiative, rather than on the basis of medical advice from a practitioner licensed by law to administer drugs. Further, AAPCC reports, published scientific and medical literature, and law enforcement reports indicate that individuals taking these SCs on their own initiative, rather than on the medical advice of a licensed practitioner.

d. 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 they will have the same potentiality for abuse as such substance, 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.

As noted by the HHS, pharmacological studies sponsored by NIDA have demonstrated that PB-22, 5F-PB-22, AB-FUBINACA and ADB-PINACA are similar to other Schedule I SCs. All four of these substances, similar to schedule I SCs, display high affinity binding and potent agonist functional activity at the cannabinoid (CB1) receptor, while drug discrimination studies have demonstrated the ability of all four substances to substitute for THC (see factor 2). The results supporting CB1 agonist activity of PB-22, and 5F-PB-22 are consistent with the similar findings reported in published literature (Banister et al., 2015).

Factor 2: Scientific Evidence of Pharmacological Effect, if Known

In vitro receptor binding and functional assays were conducted with PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA. In addition, drug discrimination assays using Sprague Dawley rats were performed to identify drugs with similar subjective effects to THC. The results are shown in Table 1. These results indicate that PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA, similar to other schedule I SCs, bind to CB1 receptors with high affinity and act as agonists at CB1 receptors.

Table 1. *In vitro* binding and functional and *in vivo* drug discrimination data for PB-22, 5F-PB-22, AB-FUBINACA and ADB-PINACA

	In vitro		***In vivo***
	Binding at CB1[3]	**Function at CB1**[4]	**Drug Discrimination**[5]
PB-22	K_i – 0.73 nM[a]	EC_{50} – 2.47 nM[b]	Full substitution (ED_{50} = 0.20 mg/kg[h])
5F-PB-22	K_i – 0.27 nM[c]	EC_{50} – 0.95 nM[d]	Full substitution (ED_{50} = 0.039 mg/kg[h])
AB-FUBINACA	K_i – 0.9 nM[e] K_i – 2.38 nM[f]	EC_{50} – 23.2 nM[e] EC_{50} – 3.0 nM[g]	Full substitution (ED_{50} = 0.18 mg/kg[h])
ADB-PINACA	K_i – 0.6 nM[i]	EC_{50} – 0.02 nM[i]	Full substitution (ED_{50} = 0.58 mg/kg[j])

[a] NIDA, 2013a; [b] NIDA, 2013b; [c] NIDA, 2013c; [d] NIDA, 2013d; [e] Buchler et al., 2009; [f] NIDA, 2013e; [g] NIDA, 2013f; [h] Gatch and Forster, 2015; [i] NIDA, 2014; [j] NIDA, 2015

[3] In vitro CB1 receptor binding assays are conducted in membrane preparations from HEK-293 cells or CHO cells that expressed human CB1 receptors with [^{3}H]CP 55940 as a radioligand.

[4] In vitro CB1 receptor functional assays for these substances with the exception of ADB-PINACA are conducted my measuring morphological responses following drug administration in CHO cells that expressed human CB1 receptors. For determination agonist functional activity of ADB-PINACA, cAMP inhibition assay was conducted using CHO cells that expressed human CB1 receptors.

[5] Discriminative stimulus effects are evaluated by the ability of test drug to substitute for the discriminative stimulus effects of THC (3 mg/kg) in rats.

The drug discrimination assay is a well-accepted animal model used to predict subjective effects of substances in humans (Schuster and Johanson, 1988; Balster and Bigelow, 2003; Tai et al., 2014). In NIDA-sponsored drug discrimination studies, PB-22, 5F-PB-22, AB-FUBINACA and ADB-PINACA, similar to other schedule I SCs (e.g., JWH-018) fully substituted for THC in animals trained to discriminate the stimulus effects of THC (3 mg/kg). Based on results from the receptor binding (Ki), CB1 functional assay, and drug discrimination studies, the HHS concluded that PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA act as full psychoactive cannabinoid agonists with no antagonist activity, and that these four substances are more potent than THC, the principal psychoactive chemical in marijuana (schedule I), and are similar in activity to JWH-018 (schedule I).

Human Studies

No human clinical studies involving PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA have been reported.

Factor 3: The State of Current Scientific Knowledge Regarding PB-22, 5F-PB-22, AB-FUBINACA and ADB-PINACA

Synthetic cannabinoids emerged in the early 1980s. They were originally designed to investigate structure activity relationships (SAR) based on the potent substance, 9-nor-9β-hydroxyhexahydrocannabinol (HHC) (Weissman et al., 1982; Melvin et al., 1984). Interest in various structural classes was generated by the mouse vas deferens (MVD) and prostaglandin synthetase activity of pravadoline and subsequent finding of affinity to the cannabinoid receptor (Huffman, 2009).

Chemistry and Physical Properties

Figure 1. Chemical Structures of PB-22, 5F-PB-22, AB-FUBINACA and ADB-PINACA

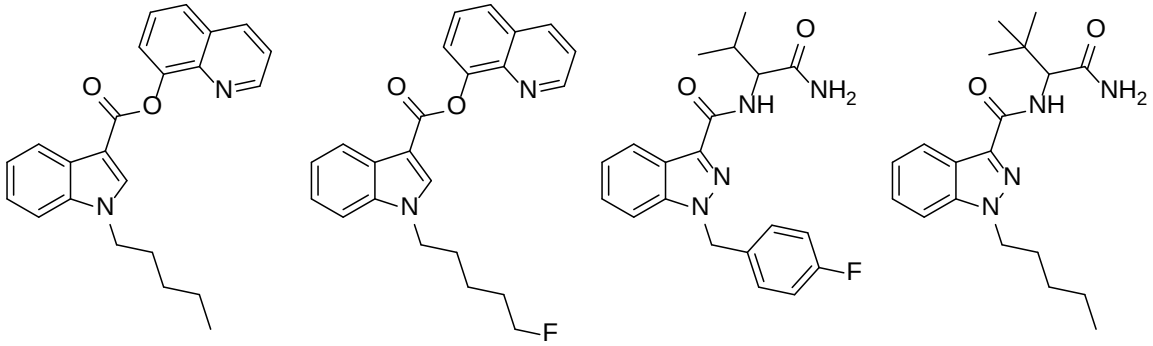


Table 2. The chemical and physical properties of quinolin-8-yl 1-pentyl-1*H*-indole-3-carboxylate

Synonyms	PB-22, QUPIC
Systemic Name (IUPAC, CAS)	Quinolin-8-yl 1-pentyl-1*H*-indole-3-carboxylate
CAS #	1400742-17-7
Chemical Formula	$C_{23}H_{22}N_2O_2$
Molecular Weight	358.4

Table 3. The chemical and physical properties of quinolin-8-yl 1-(5-fluoropentyl)-1H-indole-3-carboxylate

Synonyms	5F-PB-22, 5F-QUPIC
Systemic Name (IUPAC, CAS)	Quinolin-8-yl 1-(5-fluoropentyl)-1*H*-indole-3-carboxylate
CAS #	1400742-41-7
Chemical Formula	$C_{23}H_{21}FN_2O_2$
Molecular Weight	376.4

Table 4. The chemical and physical properties of *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide

Synonyms	AB-FUBINACA
Systemic Name (IUPAC, CAS)	*N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide
CAS #	1185282-01-2
Chemical Formula	$C_{20}H_{21}FN_4O_2$
Molecular Weight	368.4

Table 5. The chemical and physical properties of *N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide

Synonyms	ADB-PINACA
Systemic Name (IUPAC, CAS)	*N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide
CAS #	1633766-73-0
Chemical Formula	$C_{19}H_{28}N_4O_2$
Molecular Weight	344.5

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

Early studies have focused primarily on varying the indole nitrogen (1-position) and 3-position substituents. PB-22 and 5F-PB-22 (Figure 1), similar to JWH-018 and AM-2201, respectively, are substances representative of the aminoalkylindole structural class. Aminoalkylindoles are known to exhibit typical cannabinoid pharmacology *in vivo* (D'Ambra et al., 1992; Compton et al., 1992). For example, 5F-PB-22 is structurally related to AM-2201 and it differs by having 8-quinolinyloxyl replacing the naphthalene group of AM-2201. The indole core became a framework for continued investigations with the early work by Sterling-Winthrop that led to pravadoline and WIN-55212-2 (D'Ambra et al., 1992). Several other research groups expanded this investigation of structure activity relationships pertaining to this structural class (Huffman, 2009; Makriyannis and Liu, 2003). The scientific and patent literature details further modifications of the aminoalkylindole structural class with specific substitutions at the 3-position of the indole core structure to incorporate aromatic and non-aromatic ring systems. PB-22, similar to JWH-018, another schedule I SC, is based on the same indole core structure with a substitution of an alkyl group at the 1-position of the indole ring system. This alkyl group for both PB-22 and JWH-018 is a five carbon unit chain, known as a pentyl group. Both PB-22 and JWH-018 are substituted at the 3-position with a carbonyl linker to a fused aromatic ring system. In PB-22, there is an additional oxygen atom between the carbonyl group and the fused ring system. In both substances, the fused aromatic ring systems are based on ten atoms connected to each other in the same manner. In PB-22, one of these ten atoms is a nitrogen atom whereas in JWH-018, the ring system is carbon-based. Both fused rings in PB-22 and JWH-018 are aromatic, being of the same chemical classification.

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

5F-PB-22 (Figure 1) is structurally similar to the schedule I substance AM-2201. Both 5F-PB-22 and AM-2201 are based on the same indole core structure with a substitution of fluoroalkyl group at the 1-position of the indole ring system in both structures. This fluoroalkyl group for both 5F-PB-22 and AM-2201 is a five carbon unit chain, known as a pentyl group with a fluorine atom present on the terminal carbon atom. Both 5F-PB-22 and AM-2201 are substituted at the 3-position with a carbonyl linker to a fused aromatic ring system. In 5F-PB-22 there is an additional oxygen atom between the carbonyl group and the fused ring system. In both substances, the fused aromatic ring systems are based on ten atoms connected to each other in the same manner. In 5F-PB-22, one of these ten atoms is a nitrogen atom whereas in AM-2201, the ring system is carbon-based. Both fused rings in 5F-PB-22 and AM-2201 are aromatic, being of the same chemical classification.

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

AB-FUBINACA (Figure 1) shares structural features with schedule I SCs such as AKB48. Both AB-FUBINACA and AKB48 are based on the same indazole core structure with substitutions at the 1- and 3-positions of the indazole ring system. The 1-position of AB-FUBINACA is substituted with a para-fluorobenzyl group. The 3-position of AB-FUBINACA, like AKB48, is substituted with an amide linker. In AB-FUBINACA the nitrogen atom (N) of this linker is further substituted with an acyclic alkyl amide, named 1-amino-3-methyl-1-oxobutan-2-yl.

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

ADB-PINACA (Figure 1) shares structural features with the schedule I substance AKB48. ADB-PINACA and AKB48 are based on the indazole core structure and are substituted on the 1- and 3-positions of their core indazole ring system. Structurally, ADB-PINACA and AKB48 are the same with one exception. AKB48 has an adamantly group attached through an amide linkage to its indazole core. The only difference

between AKB48 and ADB-PINACA is that the adamantyl group is replaced with a 1-amino-3,3-dimethyl-1-oxobutan-2-yl group (ADB) to form ADB-PINACA.

Metabolism and Pharmacokinetics

Several publications have described the metabolism of SCs, including PB-22, 5F-PB-22, AB-FUBINACA and ADB-PINACA. Of note, as described by Vikingsson et al. (2015), there is a significant difference in the metabolites identified following incubation with cell lines such as human liver microsomes as compared to those found in authentic biological samples. The results are summarized in Table 6.

Table 6. Metabolism and pharmacokinetics using cell assay

Substance	**Pathways Observed/ Common Metabolite Observed**	**# of Metabolites Observed**	**Assay Conditions**	**Citation**
CELL ASSAYS				
PB-22/ 5F-PB-22	Ester hydrolysis; Oxidative defluorination; Epoxide formation with internal hydrolysis	20/22	Cryopreserved human hepatocytes	Wohlfarth et al., (2014)
PB-22/ 5F-PB-22	Cleavage reaction to produce indoleacetic acid type metabolites		Human liver microsomes	Takayama et al. (2014)
AB-FUBINACA	Oxidation on the N-(1-amino-alkyl-1-oxobutan) moiety		Human liver microsomes	Takayama et al. (2014)
AB-FUBINACA	Defluorobenzyl; extra unsaturation	8	Human liver microsomes	Vikingsson et al., (2015)
AB-FUBINACA	Enzymatic hydrolysis of primary amide;	7	Human liver microsomes	Thomsen et al., (2015)

	mono- and di-hydroxylation of the 1-amino-3-methyl-1-oxobutane moiety			
BIOLOGICAL SAMPLES				
AB-FUBINACA	Dealkylation; by releasing 4-fluorobenzyl; hydroxylation	3	Wistar rat urine samples	Chen et al., (2015)
AB-FUBINACA	Hydroxylation on the indole ring; hydroxylation on the amino-oxobutane moiety; dealkylation; hydrolysis of primary amide	15	Human urine samples (n=28; 25 DUID, 2 autopsy, 1 act of violence)	Vikingsson et al., (2015)
ADB-PINACA	N-pentanoic acid metabolite		Human biological samples due to overdose (n = 8)	Schwartz et al., (2015)

Medical Application

The DEA is not aware of any currently accepted medical uses for PB-22, 5F-PB-22, AB-FUBINACA, or ADB-PINACA. A letter dated November 7, 2013 was sent from the DEA Deputy Administrator to the Assistant Secretary for Health, Department for Health and Human Services as notification of intent to temporarily place these four substances in schedule I and solicited comments, including whether there was an exemption or approval in effect for the substances in question under the Federal Food, Drug and Cosmetic Act. The Assistant Secretary of Health responded that there were no current INDs or NDAs for these synthetic cannabinoids in a letter to the DEA Assistant Administrator dated January 27, 2014. The scientific and medical evaluations provided by HHS also state that PB-22, 5F-PB-22, AB-FUBINACA or ADB-PINACA have no

currently accepted medical use. These are not the subject of approved NDAs or INDs and are not currently marketed as approved drug products.

Factor 4: Its History and Current Pattern of Abuse

Synthetic cannabinoids have been developed over the last 30 years as tools for investigating the cannabinoid system (Weissman et al., 1982; Huffman et al., 1996; Huffman et al., 1999). A commercial laboratory in Frankfurt, Germany announced the identification of JWH-018 in samples of herbal incense, and others were identified shortly after this initial determination (Piggee, 2009). Synthetic cannabinoids were first reported in the U.S. in a November 2008 encounter, where a shipment of "Spice" was seized and analyzed by the U.S. Customs and Border Protection (CBP) in Dayton, Ohio. Around the same time, in December 2008, JWH-018 and cannabicyclohexanol were identified by German forensic laboratories (EMCDDA, 2009). It has been stated that there is a belief that these substances existed and were abused some time prior to their identification (Psychonaut Web Mapping Research Group, 2009). Since then, the popularity of SCs and their associated products has increased steadily as evidenced by law enforcement seizures, public health information, and media reports. Amidst multiple attempts to place SCs found on the illicit market into schedule I of the CSA, new substances of SCs intended to circumvent current legislation continue to be encountered.

Since the initial identification of JWH-018 (November 2008), many additional synthetic cannabinoids have been found applied on plant material and encountered as designer drug products (Auwarter et al., 2009; DEA, 2009). The popularity of these cannabinoids and their associated products appears to have increased since January 2010 in the U.S. based on seizure exhibits and media reports. This trend appears to mirror those experienced in Europe since 2008 (EMCDDA, 2009). Synthetic cannabinoids are being encountered in most regions of the United States with the substances found as adulterants on plant material or being abused alone as self-reported on Internet discussion boards (Atwood et al., 2010). In recent overdoses, PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA have been shown to be laced on green plant material, similar to the SCs that have been previously encountered.

The psychoactive properties of the products are directly linked to the SCs laced on the plant material (Auwarter et al., 2009; EMCDDA, 2009; Atwood et al., 2010). This was reconfirmed in a recent publication that analyzed various herbal products that contained SCs (Ogata et al., 2013). While some SCs were found to be applied to known psychoactive substances, including Cannabis sativa, Salvia divinorum, and Mitragyna speciose, except for the psychotropic plants named above, the plant material most commonly found as a carrier medium in SC-containing products was devoid of psychoactive effects. This demonstrates that the effects observed following ingestion of a SC product originate from the actual SC, and not the plant material (Ogata et al., 2013).

A major concern, as reiterated by public health officials and medical professionals, remains the targeting and direct marketing of SCs and SC-containing products to adolescents and youth (Auwarter et al., 2009; EMCDDA, 2009; Lindigkeit et al., 2009; Dresen et al., 2010; Hudson et al., 2010; Uchiyama et al., 2010; Uchiyama, 2012a; Uchiyama et al., 2012b; Oluwabasi et al., 2012; Durand et al., 2013; ONDCP, 2015). This is supported by law enforcement encounters and reports from emergency departments (SAMHSA, 2013, 2014; Fattore and Fratta, 2011; Vandrey et al., 2012); however, all age groups have been reported by media as abusing these substances and related products. Individuals, including minors, are purchasing SCs from Internet websites, gas stations, convenience stores, and head shops.

The Monitoring the Future (MTF) survey for 2014 reported that in 2012, for the first time, 8th and 10th graders were asked about their use of synthetic cannabinoids, colloquially and incorrectly referred to as “synthetic marijuana;” annual prevalence rates were 4.4% and 8.8%, respectively. Use in the 8th, 10th, and 12th grades dropped in 2013, and the decline was sharp and significant among 12th graders. The declines continued in 2014 and were significant for 10th and 12th graders. In 2014, the annual prevalence for 8th, 10th, and 12th graders was 3.3%, 5.4%, and 5.8%, respectively (Johnston et al., 2015a). In 2015, the annual prevalence for 8th, 10th, and 12th graders decreased again to 3%, 4%, and 5%, respectively (Johnston et al., 2015b). While these statistics demonstrate a decline in SC use amongst youth, hospitalizations due to serious adverse effects following ingestion of SCs, including PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA by adolescents and teens continue to occur. AAPCC reports for SCs in 2015 were the highest observed since reporting began in

2011. Reports in 2015 more than doubled compared to those shown for 2011 (See Factor 5; Table 7).

Dresen and colleagues (Dresen et al., 2010) found that SCs are being abused by individuals in drug treatment centers with a positive rate of 63.3% in forensic psychiatric centers, based on their sampling. According to recent testimony given by the Deputy Director of the Office of National Drug Control Policy (ONDCP) to the U.S. Senate Caucus on International Narcotics Control Board (September 25, 2013), current drug testing misses significant populations of SC users.[6] In an example described in this testimony, a study found that in a sample of men 30 years old or younger within the Washington, D.C. parole and probation system, 39% of those who cleanly passed a traditional drug screen tested positive for SCs.[7] The study continued to say that between one-quarter and one-third of young men who were tested in the Washington, D.C. criminal justice system had positive test results for SCs, regardless of whether they failed or passed a traditional drug screen.[8]

Smoking mixtures of these substances abused for the purpose of achieving intoxication have resulted in numerous emergency department visits and calls to poison control centers. As reported by the AAPCC, adverse effects including severe agitation, anxiety, racing heartbeat, high blood pressure, nausea, vomiting, seizures, tremors, intense hallucinations, psychotic episodes, suicide, and other harmful thoughts and/or actions can occur following ingestion of SCs. Presentations at emergency departments directly linked to the abuse of PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA have resulted in similar symptoms, including severe agitation, seizures, and/or death (Monte et al., 2013; Behonick et al., 2014; Gerostamoulos et al., 2015; Trecki et al., 2015). In addition to the characterized psychoses, driving impairment has been encountered with confirmed presence of a SC in the systems of multiple individuals, as confirmed in the scientific literature (Yeakel and Logan, 2013; Mushhoff et al., 2014; Tuv et al., 2014; Jaenicke et al., 2014; Louis et al., 2014; Karinen et al., 2015).

[6] The HHS concludes that "synthetic cannabinoids generally are not detectable in routine urine drug tests." (HHS 2015).
[7] Office of National Drug Control Policy. Community Drug Early Warning System: The CDEWS Pilot Project, 13. September 13, 2013.
[8] Id. p. vi.

As previously mentioned, these synthetic cannabinoid products are marketed directly to adolescents and youth, who appear to be the primary abusers of synthetic cannabinoids and synthetic cannabinoid-containing products. This is supported by law enforcement encounters and reports from emergency rooms (SAMHSA, 2014;[9] Fattore and Fratta, 2011; Vandrey et al., 2012); however, all age groups have been reported by media as abusing these substances and related products, as noted above. For patients between the ages of 12 – 29, 79% of drug-related emergency department visits in 2011 involved synthetic cannabinoids. In addition, the majority (65%) of emergency department visits of patients aged 20 or younger, which involved synthetic cannabinoids, did not involve any other substance. Of the remaining 35% of these individuals, the most frequently abused substances in combination with synthetic cannabinoids were marijuana (17%), pharmaceuticals (16%), and alcohol (15%) (SAMHSA, 2014). These substances and their products are commonly marketed as "legal highs" with a disclaimer that they are "not for human consumption." As detailed in reports discussed in Factor 5, law enforcement and public health officials are encountering the abuse of these substances (CDC, 2013a,b,c; NFLIS, 2015; STRIDE, 2015; STARLiMS, 2015).

Factor 5: The Scope, Duration, and Significance of abuse

PB-22 and 5F-PB-22 are synthetic cannabinoids that have pharmacological effects similar to the schedule I hallucinogen THC. PB-22 and 5F-PB-22 were not reported in the scientific literature prior to their appearance on the illicit drug market. A report from March 2013 identified PB-22 as a component of dried plant material obtained via the Internet between July 2012 and January 2013 in Japan (Uchiyama et al., 2013).

AB-FUBINACA is also a synthetic cannabinoid that has pharmacological effects similar to the schedule I hallucinogen THC. First appearing in a 2009 patent filed by the pharmaceutical manufacturer Pfizer (Buchler et al., 2009), the first report of AB-FUBINACA in the scientific literature was as a component of so-called "herbal products" purchased via the Internet in July 2012 (Uchiyama et al., 2012c).

[9] SAMHSA (the Substance Abuse and Mental Health Services Administration) is a branch of the U.S. Department of Health and Human Services. It is charged with improving the quality and availability of prevention, treatment, and rehabilitative services in order to reduce illness, death, disability, and cost to society resulting from substance abuse and mental illnesses.

ADB-PINACA was first encountered in the United States following reports of serious adverse events in Georgia on August 23, 2013. Reports of ADB-PINACA were not found in the scientific literature prior to its emergence on the designer drug market. The Georgia Bureau of Investigation (GBI) reported on September 12, 2013, that ADB-PINACA, was detected in "herbal incense" products sold under the brand name "Crazy Clown." It was later confirmed by the Centers for Disease Control and Prevention (CDC) as the substance responsible for severe adverse events in at least 22 persons who consumed the product (CDC, 2013b). In addition, on August 30, 2013, the Colorado Department of Public Health and Environment (CDPHE) was notified by several hospitals of an increase in the number of patients visiting their emergency departments (EDs) with altered mental status after using synthetic cannabinoids (Appendix 2). On September 8, 2013, the CDPHE, with the assistance of the CDC, began an epidemiologic investigation whereby 221 cases of severe illness due to ingestion of a synthetic cannabinoid were identified (CDC, 2013c). Those that presented at emergency rooms in the Denver, Colorado area around September 1, 2013 had symptoms similar to those found in the August 2013 Georgia incident. Laboratory analysis of samples from the Colorado incident confirmed that the substance abused in the "herbal incense" products was ADB-PINACA.

The National Forensic Laboratory Information System (NFLIS)[10] is a program of the DEA that collects drug identification results from drug cases analyzed by other federal, state, and local forensic laboratories. The NFLIS data up to November 30, 2015 were queried on December 23, 2015 for PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA (data are still being reported for August – November 2015, due to normal lag time for laboratories to report to NFLIS) (Table 8, 9, Appendix 1).

The System to Retrieve Information from Drug Evidence (STRIDE)[11] collected the results of drug evidence analyzed at DEA laboratories and reflects evidence submitted by the DEA, other federal law enforcement agencies, and some local law enforcement agencies. STRIDE data was queried through September 30, 2014, by date submitted to Federal forensic

[10] NFLIS is a national drug forensic laboratory reporting system that systematically collects results from drug chemistry analyses conducted by state and local forensic laboratories across the country.
[11] STRIDE is a database of drug exhibits sent to DEA laboratories for analysis. Exhibits from the database are from the DEA, other federal agencies, and some local law enforcement agencies.

laboratories. On October 1, 2014, STARLiMS replaced STRIDE as the DEA laboratory drug evidence data system of record. DEA laboratory data submitted after September 30, 2014, are reposited in STARLiMS. (STARLiMS data were queried through November 30, 2015) (Table 10, Appendix 1).

Poison control centers continue to report the abuse of SCs and their associated products. These substances remain a threat to both the short- and long-term public health and safety. Exposures to SCs were first reported to the AAPCC in 2011 (Table 7). The AAPCC report published on April 23, 2015, showed a marked spike in poison center exposure calls throughout the United States in 2015. The AAPCC reported 1,512 exposure calls in April 2015, representing an almost three-fold increase in exposures to SCs as compared to the previous largest monthly tally (657 exposures in January 2012) since reporting began in 2011. For the first time since reporting began by the AAPCC in 2011, the number of cases in 2015 has dramatically risen, more than doubling those reported in 2014. The numbers of cases reported in 2015 were the highest ever recorded. In addition, a majority of exposure incidents from 2011 to the present resulted in individuals seeking medical attention at health care facilities.[12]

Table 7. Exposure cases of synthetic cannabinoids as reported to poison centers*

YEAR	# OF CASES
2011	6,968
2012	5,230
2013	2,668
2014	3,682
2015* (through December 31, 2015)	7,779

* AAPCC, January, 2016

[12] The content of this report does not necessarily reflect the opinions or conclusions of the American Association of Poison Control Centers (AAPCC). AAPCC (http://www.aapcc.org) maintains the national database of information logged by the country's 57 Poison Control Centers (PCCs). Case records in this database are from self-reported calls: they reflect only information provided when the public or healthcare professionals report an actual or potential exposure to a substance (e.g. an ingestion, inhalation, topical exposure, etc.) or request information/educational materials. Exposures do not necessarily represent a poisoning or overdose. The AAPCC is not able to completely verify the accuracy of every report made to member centers. Additional exposures may go unreported to PCCs and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance(s).

Table 8. Reports obtained through the NFLIS database[§]

NFLIS[* §]					
DRUG	**2012 REPORTS‡**	**2013 REPORTS‡**	**2014 REPORTS[‡]**	**2015 REPORTS[‡]**	**STATES**
PB-22	0	1,898 (January)	1,911	126	AL, AR, AZ, CO, CT, FL, GA, HI, IA, ID, KS, KY, LA, MA, MD, MN, MO, MS, ND, NE, NH, NJ, NM, NV, NY, OH, OK, OR, PA, SC, TN, TX, UT, VA, WA, WI, WV, WY
5F-PB-22	0	1,828 (January)	978	209	AR, AZ, CA, CO, CT, FL, GA, IA, ID, IL, IN, KS, KY, LA, MA, MD, MN, MO, MS, ND, NE, NH, NJ, NM, NV, NY, OH, OK, OR, PA, SC, TN, TX, UT, VA, WI, WV, WY
AB-FUBINACA	1 (July)	2,168	5,789	1,641	AL, AR, AZ, CA, CO, CT, FL, GA, HI, IA, ID, IL, IN, KS, KY, LA, MA, MD, MN, MO, MS, ND, NE, NH, NJ, NM, NV, NY, OH, OK, OR, PA, SC, TN, TX, UT, VA, WA, WI, WV, WY
ADB-PINACA	0	75 (August)	389	123	CO, GA, ID, IN, KS, LA, MD, NH, NJ, OK, PA, VA, WI

* Query date: December 23, 2015.

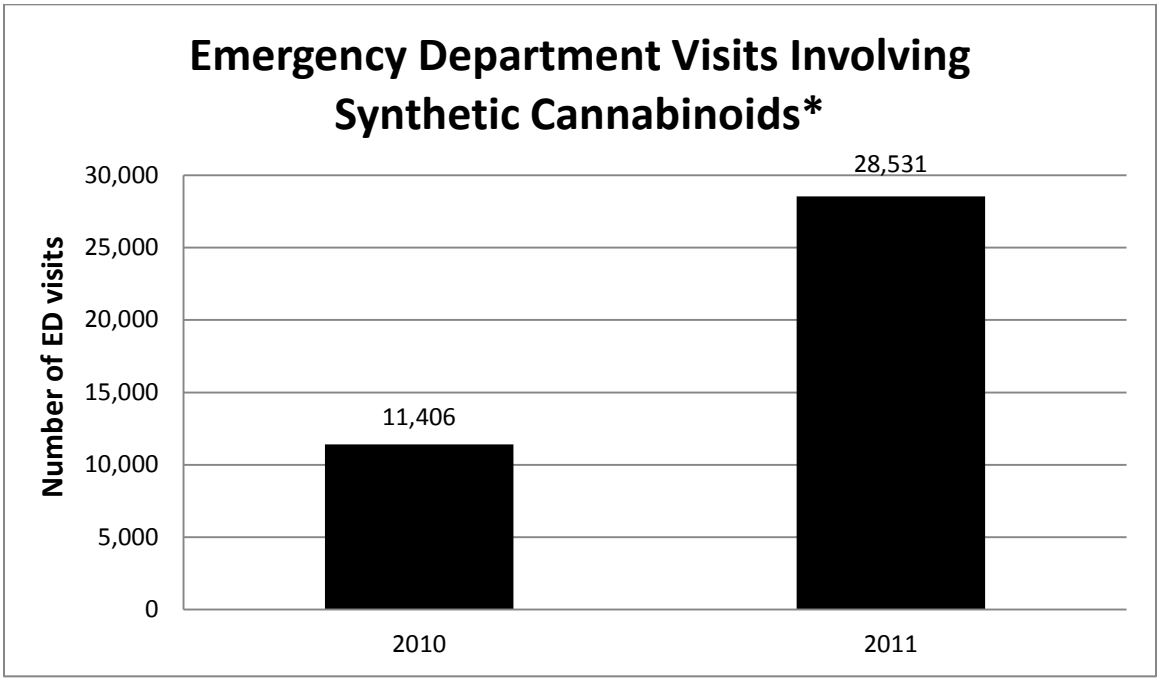
‡ The month in parenthesis (e.g., (March)) corresponds to the month the substance was first encountered.

§ Laboratories reporting to NFLIS include State, local and other federal laboratories (not including DEA).

In 2010, the Substance Abuse and Mental Health Services Administration (SAMHSA) reported 11,406 emergency department visits involving synthetic cannabinoid products (SAMHSA, 2012). In 2011, SAMHSA reported the number of emergency department visits involving synthetic cannabinoid products had increased 2.5 times to 28,531 (SAMHSA, 2013) (Figure 2).

Synthetic cannabinoids and the associated products are sold over the Internet and found to be abused by diverse populations. The scientific literature and reports received by the DEA suggest that tolerance and dependence to synthetic cannabinoids may develop (Zimmermann et al., 2009). In addition, the chronic abuse of products laced with synthetic cannabinoids has been linked to addiction and withdrawal (Vardakou et al., 2010). Chronic abuse of synthetic cannabinoids has been linked to signs of addiction and withdrawal similar to that experienced with cannabis abuse (Zimmermann et al., 2009; Muller et al., 2010; Vardakou et al., 2010). Additionally, tolerance to these drugs may develop fairly rapidly with larger doses being required to achieve the desired effect (EMCDDA, 2009).

Figure 2. Emergency department visits involving synthetic cannabinoids (SAMHSA, 2013). Synthetic cannabinoid data were not collected prior to 2010.



*Estimates of ED visits are based on a representative sample of non-Federal, general, short-stay hospitals with 24-hour EDs in the U.S.

As mentioned by the HHS, in May of 2014, clusters of cases of adverse health effects or severe toxic effects with synthetic cannabinoid product use were reported in Austin, TX (>20 cases) and Dallas, TX (>100 cases) (Trecki et al., 2015). Each of these two reported Texas clusters identified AB-FUBINACA and XLR11 (schedule I) among

the substances ingested (Trecki et al., 2015).[13] More importantly, deaths associated directly with AB-FUBINACA use were reported in Colorado (Trecki et al., 2015) and Texas (Texas Medical Examiner, 2014).

Two clusters of outbreaks in Georgia and Colorado, describing altered mental status, implicated ADB-PINACA as being present in multiple brands of synthetic cannabinoid containing products (Schwartz et al., 2014; Trecki et al. 2015).

In addition, a report sent to the DEA from the Mansfield Division of Police Forensic Science Laboratory in Mansfield, Ohio, has confirmed the presence of PB-22 (17 cases) or 5F-PB-22 (6 cases) from January through May of 2013.

A recent (June 12, 2015) Morbidity and Mortality Weekly Report (MMWR) from the Centers for Disease Control and Prevention (CDC) indicated that, on April 6, 2015, the CDC received notification of an increase in the number of telephone calls to U.S. poison centers related to synthetic cannabinoid use. Monthly calls to all AAPCC member poison centers are tracked by the National Poison Data System (NPDS). After the initial notification, the CDC reviewed information from the NPDS on reported adverse health effects related to synthetic cannabinoid use for the period January through May 2015. During this time, poison centers reported 3,572 calls related to synthetic cannabinoid use, a 229% increase from the 1,085 calls reported during the corresponding (January through May) period in 2014. The number of calls increased significantly in mid-April before decreasing nearly to 2014 levels by the end of May (CDC, 2015). The CDC MMWR further suggested that the increased number of synthetic cannabinoid variations along with higher toxicities may suggest a heightened public health threat than in previous years (CDC, 2015).

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

As stated by the HHS, based solely on its pharmacological similarity to JWH-018 and THC and its potency, the subjective risks to the public health of PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA are similar to those of other cannabinoids, which

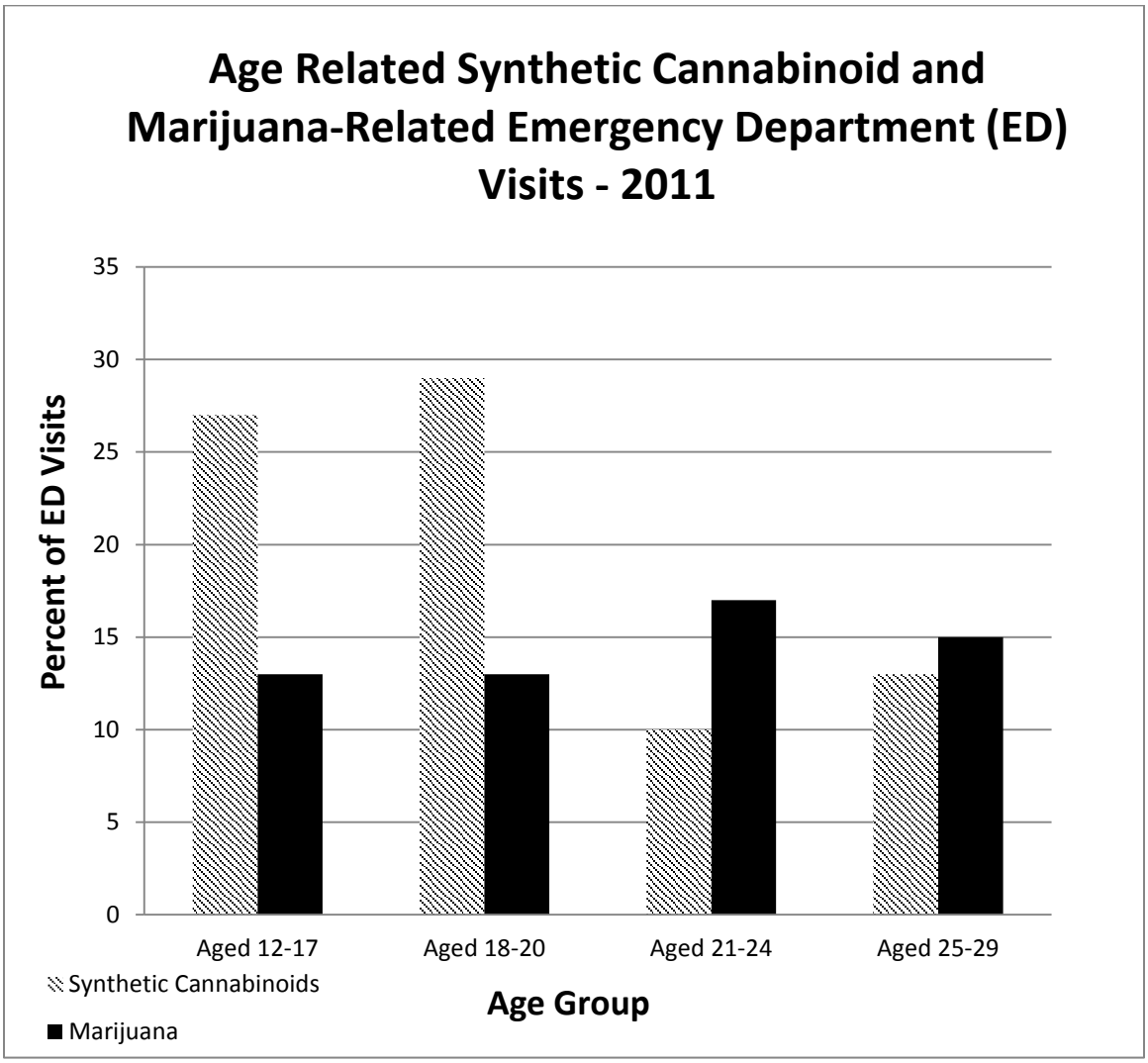
[13] A causative association between the substance identified and subjective/objective harms could not be determined, since the identification was based on information from local law-enforcement seizures during the same period.

are controlled in schedule I of the CSA. Law enforcement and public health officials have reported exposure incidents that demonstrate the dangers associated with abuse of synthetic cannabinoids to both the individual abusers and other affected individuals. Warnings regarding the dangers associated with abuse of synthetic cannabinoids and their products have been issued by numerous state public health departments and poison control centers and private organizations. Some of the common clinical effects reported in emergency rooms in response to the abuse of synthetic cannabinoids include vomiting, anxiety, agitation, irritability, seizures, hallucinations, tachycardia, elevated blood pressure, and loss of consciousness (Forrester et al., 2011; Cohen et al., 2012; Harris and Brown, 2013; Hermanns-Clausen et al., 2013; Zawilska and Wojcieszak, 2013).

A 12-month study conducted in 2012 demonstrated that out of 950 self-reported users, 2.4% reported having a medical emergency requiring treatment resulting from a combination of panic, anxiety, paranoia, and breathing difficulties (Winstock and Barratt, 2013). Data from this study also demonstrated that recent users who reported seeking emergency treatment were significantly younger than those who did not report seeking treatment (Winstock and Barratt, 2013). These data correspond to figures reported by SAMHSA, which demonstrates that youth, specifically those aged 12 to 17 years and those aged 18 to 20 years, comprise a large percentage of users requiring emergency medical attention (Figure 3).

A more recent study by Bonar et al. (2014) reported that participants had multiple motives for using SCs including included: curiosity (91%), feeling good/getting high (89%), relaxation (71%), and getting high without having a positive drug test (71%).

Figure 3. Age-related emergency department visits involving synthetic cannabinoids and marijuana (SAMHSA, 2014).



As stated by the HHS, although related pharmacologically to THC, the active ingredient in marijuana, the synthetic cannabinoids are two to three times more likely to be associated with sympathomimetic effects (e.g. tachycardia and hypertension), and approximately five times more likely to be associated with hallucinations (Forrester et al., 2011).

Since abusers obtain these drugs through unknown sources, purity of these drugs is uncertain, thus posing significant adverse health risk to these users (EMCDDA, 2009; Dresen et al., 2010; Guglemann et al., 2014). At least ten deaths have been reported involving these

substances: PB-22 (3 deaths) (Gerostamoulos et al., 2015); 5F-PB-22 (5 deaths) (Behonick et al., 2014; Santacroce et al., 2015); AB-FUBINACA (1 death) (Trecki et al., 2015) or ADB-PINACA (1 death) (Trecki et al., 2015). There are also reported instances of emergency department admissions in association with the abuse of PB-22 and 5F-PB-22. Additional deaths involving a variety of SCs have been reported, along with additional instances of severe toxic effects following ingestion of SCs (Trecki et al., 2015).

As mentioned above, in late August 2013, local law enforcement in Brunswick, Georgia, reported that 22 individuals presented to emergency departments with severe adverse reactions after the consumption of a synthetic product called "Crazy Clown" (Schwartz et al., 2015). Adverse effects included anxiety, delirium, psychosis and aggressive behaviors. The substance responsible for these effects was later identified by the GBI as ADB-PINACA. Days later, in early September 2013, over 200 patients presented to emergency departments in Colorado had adverse reactions to a synthetic product labeled as "Black Mamba" (Appendix 2). Adverse effects included having no gag reflex, inability to breathe on their own, hallucinations, and psychotic episodes as described by nurses and attending physicians (Monte et al., 2014). The substance in these episodes was also identified as ADB-PINACA.

Factor 7: Its Psychic or Physiological Dependence Liability

As stated by the HHS, PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA have pharmacological profiles that are similar to other schedule I SCs. Thus it is reasonable to assume that PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA possess physiological and psychological dependence liability that is similar to that of other schedule I cannabinoids (THC and JWH-018).

The HHS also stated that the terminology "cannabis withdrawal" is described by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The following signs and symptoms occur within approximately 1 week: irritability; anger; aggression; nervousness or anxiety; sleep difficulty (e.g., insomnia, disturbing dreams); decreased appetite or weight loss; restlessness; depressed mood; at least one of the following physical symptoms causing significant discomfort: abdominal pain,

shakiness/tremors, sweating, fever, chills, or headache (DSM-5, American Psychiatric Association, 2013, Gorelick et al., 2012). The HHS also mentioned that because PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA share pharmacological similarity to THC, the active principle in cannabis, it is likely that these substances possess potential to produce similar withdrawal symptoms.

Every-Palmer (2010) has reported of the recurrence of psychosis in stable individuals with a previous history of psychosis. Every-Palmer (2011) followed up the initial communication with interviews of 15 patients with severe mental illness in a New Zealand forensic and rehabilitation service. In a case report, dependence syndrome corresponding to the ICD-10 and DSM-IV criteria and the physical withdrawal resembled cannabis dependence (Zimmermann et al., 2009) after the consumption of "Spice Gold." Spice Gold has been found to contain the substance JWH-018. While PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA are pharmacologically related to JWH-018, no studies regarding the psychic or physiological dependence liability of PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA have been identified.

Factor 8: Whether the Substance is an Immediate Precursor of a Substance Already Controlled

PB-22, 5F-PB-22, AB-FUBINACA and ADB-PINACA are not considered an immediate precursor of any controlled substance of the CSA as defined by 21 U.S.C 802(23).

III. Findings for Schedule Placement Pursuant to 21 U.S.C. 812(b)

21 U.S.C. 812(b) requires the evaluation of a substance's abuse potential, accepted medical use, and safety for use under medical supervision for scheduling under the CSA as a controlled substance. After consideration of the above eight factors determinative of control of a substance (21 U.S.C. 811(c)), and a review of the scientific and medical evaluation and scheduling recommendation provided by the HHS, the DEA finds that PB-22, 5F-PB-22,

AB-FUBINACA and ADB-PINACA meet the following criteria for placement in schedule I of the CSA pursuant to 21 U.S.C. 812 (b)(1).

1) PB-22, 5F-PB-22, AB-FUBINACA and ADB-PINACA have a high potential for abuse that is comparable to other schedule I substances such as THC and JWH-018.

PB-22, 5F-PB-22, AB-FUBINACA and ADB-PINACA are synthetic substances that produce cannabinoid-like pharmacological effects that are similar to those produced by schedule I substances such as THC and JWH-018 and other synthetic cannabinoids. The pharmacological similarity of PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA to THC makes it reasonable to assume that their potential for abuse is high and would be similar to that of JWH-018, which is controlled in schedule I of the CSA. NFLIS details over 17,136 reports from forensic laboratories identifying PB-22, 5F-PB-22, AB-FUBINACA and ADB-PINACA for a period from July 2012 through December 2015. In addition, STRIDE and STARLiMS have 2,091 reports involving PB-22, 5F-PB-22, AB-FUBINACA and ADB-PINACA from February 2013 through November 2015.

2) PB-22, 5F-PB-22, AB-FUBINACA and ADB-PINACA have no currently accepted medical use in treatment in the United States.

According to the HHS, there are no approved NDAs for PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA in the United States. There are no known medical uses for PB-22, 5F-PB-22, AB-FUBINACA and ADB-PINACA. Therefore, PB-22, 5F-PB-22, AB-FUBINACA and ADB-PINACA have no currently accepted medical use in the United States.

3) There is a lack of accepted safety for use of PB-22, 5F-PB-22, AB-FUBINACA and ADB-PINACA under medical supervision.

Because PB-22, 5F-PB-22, AB-FUBINACA and ADB-PINACA have no approved medical use and have not been thoroughly investigated as new drugs, their safety for use

under medical supervision is not determined. Thus, there is a lack of accepted safety for use of these substances under medical supervision.

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Appendix 1

Public Health

1. Monitoring the Future study results for 2015 (released on December 16, 2015) state that the use of synthetic cannabinoids (SCs) fell by a statistically significant amount in 2015 for the three grades combined. The proportions reporting any use of synthetic cannabinoid products in the past 12 months now stand at 3%, 4%, and 5% in grades 8, 10, and 12, respectively. These values are down considerably from 4%, 9%, and 11% for the same grades in 2012.
2. Health effects from the drug can be life-threatening and can include (AAPCC, 2015):
    a. Severe agitation and anxiety.
    b. Fast, racing heartbeat and higher blood pressure.
    c. Nausea and vomiting.
    d. Muscle spasms, seizures, and tremors.
    e. Intense hallucinations and psychotic episodes.
    f. Suicidal and other harmful thoughts and/or actions.
    http://www.aapcc.org/alerts/synthetic-marijuana/
3. Synthetic cannabinoids, commonly known as "synthetic marijuana," "K2," or "Spice," are often sold in legal retail outlets as "herbal incense" or "potpourri." They are labeled "not for human consumption" to mask their intended purpose and avoid Food and Drug Administration (FDA) regulatory oversight of the manufacturing process. (Office of National Drug Control Policy, 2015)
4. At least 43 States have taken action to control one or more synthetic cannabinoids. (Office of National Drug Control Policy, 2015)
5. "Synthetic cannabinoid" users report experiences similar to those produced by marijuana—elevated mood, relaxation, and altered perception—and in some cases the effects are even stronger than those of marijuana. Some users report psychotic effects like extreme anxiety, paranoia, and hallucinations. (National Institute on Drug Abuse, 2015)
6. "Synthetic cannabinoid" abusers who contacted Poison Control Centers report symptoms that include rapid heart rate, vomiting, agitation, confusion, and hallucinations. "Synthetic cannabinoid" abuse can also raise blood pressure and cause reduced blood supply to the heart (myocardial ischemia), and in a few cases it has been associated with heart attacks. Regular users may experience withdrawal and addiction symptoms. (National Institute on Drug Abuse, 2015)
7. CESAR FAX, a publication from the Center for Substance Abuse Research at the University of Maryland (College Park), reported the results from Bonar et al. (2014) describing the results of the study of patients in a Midwestern residential treatment program. Results demonstrated that 71% of those reporting synthetic cannabinoid abuse used a SC-laced product to avoid a positive drug test. The two most common reasons for SC use was "curiosity" (91%) and "to feel good or get high" (89%) (September, 2014).

Table 9. NFLIS – State, Local, and Other Federal Forensic Laboratory Reports (Query date: December 23, 2015)**

	2010				2011				2012				2013			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
JWH-018; JWH-073; JWH-200; CP-47,497; CP-47,497 C8 homologue	138	413	670	1,197	1,515	994	659	536	427	342	234	150	110	97	84	57
UR-144; XLR11; AKB48	1*	0	0	0	0	0	0	50	548	3,369	6,332	5,285	6,741	6,665	4,050	2,942
PB-22	0	0	0	0	0	0	0	0	0	0	0	0	248	524	636	490
5F-PB-22	0	0	0	0	0	0	0	0	0	0	0	0	106	485	729	508
AB-FUBINACA	0	0	0	0	0	0	0	0	0	0	1	0	0	9	716	1,443
ADB-PINACA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	64	11

* Encounter confirmed in March 2012

** Data queried through November 30, 2015

Shaded box corresponds to date substance was controlled via the CSA

	2014				2015				2010-2015
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4‡ (OCT-NOV)	TOTAL
JWH-018; JWH-073; JWH-200; CP-47,497 CP-47,497 C8 homologue	69	34	22	11	28	11	9	6	7,813
UR-144; XLR11; AKB48	3,706	3,249	2,711	1,917	1,847	1,913	1,173	190	52,688
PB-22	781	623	357	150	69	32	21	4	3,935
5F-PB-22	382	269	193	134	99	83	25	2	3,015
AB-FUBINACA	2,086	1,843	1,237	623	561	708	341	31	9,599
ADB-PINACA	0	12	171	206	72	39	9	3	587

‡Data queried through November 30, 2015

Shaded box corresponds to date substance was controlled via the CSA

Table 10. STRIDE and STARLiMS Records - January 2013 through November 2015* (Query date: December 22, 2015):**

	NUMBER OF RECORDS
PB-22	630
5F-PB-22	553
AB-FUBINACA	903
ADB-PINACA	5

* No reports identified in STRIDE regarding PB-22 or 5F-PB-22 prior to February 2013. No reports of AB-FUBINACA prior to June 2013. No reports of ADB-PINACA prior to February 2014.
** Data were queried through November 30, 2015

Appendix 2

Table 11. Reports from ADB-PINACA overdoses (August – September 2013)*

Location	Substance Identified	Packet Label	Remarks
Denver, CO	ADB-PINACA	Crazy Clown Pineapple Express	None
Denver, CO	ADB-PINACA	Crazy Clown	Two males passed out in a vehicle; both became extremely ill; driver placed on life support
Denver, CO	ADB-PINACA	AM-HI-C; Atomic Bomb; Black Mamba	Single vehicle accident, driver passed out while driving and collided with a tree
Denver, CO	ADB-PINACA	Dead Man Walking	User became ill after using substance and required hospitalization
Denver, CO	ADB-PINACA	Unknown	User was found slumped over the wheel of a vehicle in the middle of an intersection
Denver, CO	ADB-PINACA	Mamba	Male and female user found passed out in backyard; female vomited over herself; male became combative and required restraints
Denver, CO	ADB-PINACA	Mamba	User had minimal vitals upon EMS arrival; required use of a respirator at hospital; user collapsed following single puff from a rolled cigarette of "Mamba"
Denver, CO	ADB-PINACA	Mamba	Two juveniles required hospitalization after smoking mamba; one juvenile found stumbling down the street

* Communication from Aurora Police Department to the DEA (December 18, 2013)

Table 12. Select Encounters of the 4 substances reported by Customs and Border Protection (January 2013 – April 2015)

Date of Detention	Identified Substance(s)	Detained at	Originated from	Destination	TOTAL WEIGHT
1/29/2013	PB-22	FedEx Anchorage, AK	China	Fort Lauderdale, FL	15 kg
1/29/2013	PB-22	FedEx Anchorage, AK	China	Fort Lauderdale, FL	15 kg
2/8/2013	PB-22	San Francisco Intl Mail	China	Richardson, TX	2 kg
2/13/2013	PB-22	San Francisco Intl Mail	China	San Dimas, CA	2 kg
2/28/2013	PB-22	San Francisco Intl Mail	China	Newman Lake, WA	300 grams
2/28/2013	PB-22	San Francisco Intl Mail	China	Newman Lake, WA	300 grams
2/28/2013	PB-22	San Francisco Intl Mail	China	Arlington, TX	100 grams
3/6/2013	PB-22	San Francisco Intl Mail	China	Tulsa, OK	2 kg
3/13/2013	PB-22	FedEx Anchorage, AK	China	South Charleston, WV	3.5 kg
3/22/2013	5-fluoro-PB-22	FedEx Anchorage, AK	China	Columbia, MO	3.5 kg
4/4/2013	PB-22	San Francisco Intl Mail	China	Phoenix, AZ	200 grams
4/4/2013	PB-22	San Francisco Intl Mail	China	Temecula, CA	2 kg
4/4/2013	PB-22	San Francisco Intl Mail	China	Columbia, MO	2 kg

4/4/2013	PB-22	San Francisco Intl Mail	China	Columbia, MO	2 kg
4/4/2013	PB-22	San Francisco Intl Mail	China	Walnut, CA	2 kg
4/12/2013	5-fluoro-PB-22	San Francisco Intl Mail	China	Phoenix, AZ	unknown
4/19/2013	PB-22	San Francisco Intl Mail	China	Sprints, LA	100 grams
5/6/2013	PB-22	San Francisco Intl Mail	China	Decatur, IL	100 grams
5/16/2013	PB-22	San Francisco Intl Mail	China	Las Cruces, NM	1 gram
5/18/2013	5-fluoro-PB-22	San Francisco Intl Mail	Hong Kong	Las Vegas, NV	500 grams
5/31/2013	5-fluoro-PB-22	FedEx Anchorage, AK	China	Las Cruces, NM	1 kg
6/13/2013	PB-22	San Francisco Intl Mail	China	Coeur D'Alene, ID	500 grams
6/13/2013	PB-22	San Francisco Intl Mail	China	Baytown, TX	1 kg
6/25/2013	PB-22	San Francisco Intl Mail	Hong Kong	Salt Lake City, UT	5 kg
6/25/2013	PB-22	San Francisco Intl Mail	China	Houston, TX	2 kg
6/25/2013	PB-22	San Francisco Intl Mail	China	Chatsworth, CA	1 kg
6/25/2013	PB-22	San Francisco Intl Mail	China	Katy, TX	3 kg
6/27/2013	5-fluoro-PB-22	FedEx Anchorage, AK	China	Las Vegas, NV	3 kg

6/29/2013	5-fluoro-PB-22	FedEx Anchorage, AK	China	Puerto Rico	2.8 kg
7/5/2013	5-fluoro-PB-22	San Francisco Intl Mail	China	Pahrump, NV	1 kg
7/5/2013	PB-22	San Francisco Intl Mail	China	Tacoma, WA	3 kg
7/8/2013	5-fluoro-PB-22	San Francisco Intl Mail	China	Las Vegas, NV	2 kg
7/8/2013	5-fluoro-PB-22	San Francisco Intl Mail	China	Las Vegas, NV	2 kg
7/10/2013	5-fluoro-PB-22	San Francisco Intl Mail	China	Anchorage, AK	1 kg
7/17/2013	5-fluoro-PB-22	San Francisco Intl Mail	China	Las Cruces, NM	300 grams
7/17/2013	5-fluoro-PB-22	San Francisco Intl Mail	China	Independence, LA	700 grams
7/17/2013	5-fluoro-PB-22	San Francisco Intl Mail	China	Independence, LA	700 grams
7/17/2013	5-fluoro-PB-22	San Francisco Intl Mail	China	Independence, LA	2.5 kg
8/8/2013	5-fluoro-PB-22	San Francisco Intl Mail	China	Houston, TX	3 kg
8/15/2013	5-fluoro-PB-22	San Francisco Intl Mail	China	Ogden, UT	500 grams
8/22/2013	PB-22	San Francisco Intl Mail	China	Elizabeth, NJ	5.5 kg
9/4/2013	5-fluoro-PB-22	FedEx Anchorage, AK	China	Tulsa, OK	2.3 kg
9/5/2013	5-fluoro-PB-22	San Francisco Intl Mail	China	Baton Rouge, LA	50 grams

10/3/2013	5-fluoro-PB-22	San Francisco Intl Mail	unknown	unknown	1.3 kg
10/9/2013	5-fluoro-PB-22	San Francisco Intl Mail	China	Bremerton, WA	2 kg
10/9/2013	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	5 kg
10/23/2013	AB-FUBINACA	ND Port of Entry	China	Unknown	
10/24/2013	5-fluoro-PB-22	San Francisco Intl Mail	China	Casper, WY	800 grams
10/24/2013	5-fluoro-PB-22	San Francisco Intl Mail	China	Bremerton, WA	2 kg
10/24/2013	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	4 kg
10/24/2013	AB-FUBINACA	San Francisco Intl Mail	China	Anderson, SC	10 grams
10/25/2013	5-fluoro-PB-22	San Francisco Intl Mail	China	Silverdale, WA	2 kg
10/31/2013	AB-FUBINACA	San Francisco Intl Mail	China	Austin, TX	5 grams
11/7/2013	AB-FUBINACA	San Francisco Intl Mail	China	Metairie, LA	100 grams
11/7/2013	AB-FUBINACA	San Francisco Intl Mail	China	Canyon Country, CA	2 kg
11/7/2013	AB-FUBINACA	San Francisco Intl Mail	China	Canoga Park, CA	3 kg
11/7/2013	AB-FUBINACA	San Francisco Intl Mail	China	Canyon Country, CA	2 kg
11/7/2013	AB-FUBINACA	San Francisco Intl Mail	China	Mchenny, IL	5 grams

11/27/2013	5-fluoro-PB-22	San Francisco Intl Mail	China	Spring, TX	5 kg
11/27/2013	5-fluoro-PB-22	San Francisco Intl Mail	China	Spring, TX	5 kg
11/27/2013	5-fluoro-PB-22	San Francisco Intl Mail	China	Houston, TX	5 kg
11/27/2013	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	5 kg
11/27/2013	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	5 kg
11/27/2013	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	5 kg
12/5/2013	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	4 kg
12/5/2013	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	4 kg
12/5/2013	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	4 kg
12/11/2013	AB-FUBINACA	San Francisco Intl Mail	China	Denton, TX	1 kg
12/18/2013	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	5 kg
12/18/2013	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	3 kg
12/19/2013	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	5 kg
12/19/2013	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	5 kg
12/19/2013	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	5 kg

12/19/2013	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	5 kg
12/19/2013	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	5 kg
1/2/2014	5-fluoro-PB-22	San Francisco Intl Mail	China	Las Vegas, NV	500 grams
1/2/2014	5-fluoro-PB-22	San Francisco Intl Mail	China	Austin, TX	1 kg
1/3/2014	5-fluoro-PB-22	San Francisco Intl Mail	China	Lakewood, WA	unknown
1/3/2014	5-fluoro-PB-22	San Francisco Intl Mail	China	Silverdale, WA	2 kg
1/3/2014	5-fluoro-PB-22	San Francisco Intl Mail	China	Lubbock, TX	2 kg
1/3/2014	5-fluoro-PB-22	San Francisco Intl Mail	China	Las Vegas, NV	2 kg
1/9/2014	5-fluoro-PB-22	San Francisco Intl Mail	China	Las Vegas, NV	1 kg
1/9/2014	5-fluoro-PB-22	San Francisco Intl Mail	China	Las Vegas, NV	1 kg
1/9/2014	5-fluoro-PB-22	San Francisco Intl Mail	China	Las Vegas, NV	1 kg
1/16/2014	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	5 kg
1/16/2014	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	5 kg
1/16/2014	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	5 kg
1/16/2014	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	5 kg

1/16/2014	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	5 kg
1/23/2014	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	5 kg
1/23/2014	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	5 kg
1/28/2014	AB-FUBINACA	FedEx Anchorage, AK	China	Coyay, Puerto Rico	1.2 kg
1/30/2014	AB-FUBINACA	San Francisco Intl Mail	China	Port Neches, TX	5 grams
1/30/2014	5-fluoro-PB-22	San Francisco Intl Mail	China	Fayetteville, AR	60 grams
1/30/2014	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	5 kg
2/6/2014	AB-FUBINACA	San Francisco Intl Mail	China	Chatsworth, CA	2 kg
2/27/2014	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	3 kg
2/27/2014	AB-FUBINACA	San Francisco Intl Mail	China	Spring, TX	3 kg
2/27/2014	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	3 kg
2/27/2014	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	3 kg
2/27/2014	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	4 kg
3/6/2014	AB-FUBINACA	San Francisco Intl Mail	China	Houston, TX	6 kg
3/20/2014	5-fluoro-PB-22	San Francisco Intl Mail	China	Chapparal, NM	1 kg

3/21/2014	AB-FUBINACA	San Francisco Intl Mail	China	Big Spring, TX	10 grams
5/8/2014	5-fluoro-PB-22	San Francisco Intl Mail	China	New Orleans, LA	50 grams
7/31/2014	5-fluoro-PB-22	San Francisco Intl Mail	Hong Kong	Trumbull, CT	1 kg
8/6/2014	5-fluoro-PB-22	San Francisco Intl Mail	China	Richmond, TX	375 grams
8/26/2014	5-fluoro-PB-22	San Francisco Intl Mail	China	Lake Jackson TX	250 grams
10/30/2014	5-fluoro-PB-22	San Francisco Intl Mail	China	Garyville, LA	300 grams
12/2/2014	5-fluoro-PB-22	San Francisco Intl Mail	China	Denver, CO	2 kg
12/9/2014	5-fluoro-PB-22	San Francisco Intl Mail	China	Denver, CO	1 kg
12/9/2014	PB-22	San Francisco Intl Mail	China	McAllen, TX	1 kg
12/16/2014	5-fluoro-PB-22	San Francisco Intl Mail	China	Kansas City, KS	50 grams
4/15/2015	AB-FUBINACA	San Francisco Intl Mail	China	Aransas Pass, TX	100 grams