DRUG ENFORCEMENT ADMINISTRATION

Drug & Chemical Evaluation Section

May 4, 2023

About the Section

- Section is part of Diversion Operations
- Consists of three Units
  - Drug & Chemical Control Unit
  - Data Analysis Unit
  - Schedule I Researcher and International Control Unit
- Section consists of senior scientists: chemists, pharmacologists, drug science specialists, toxicologist, epidemiologist, and statistician

Overview

Activities:

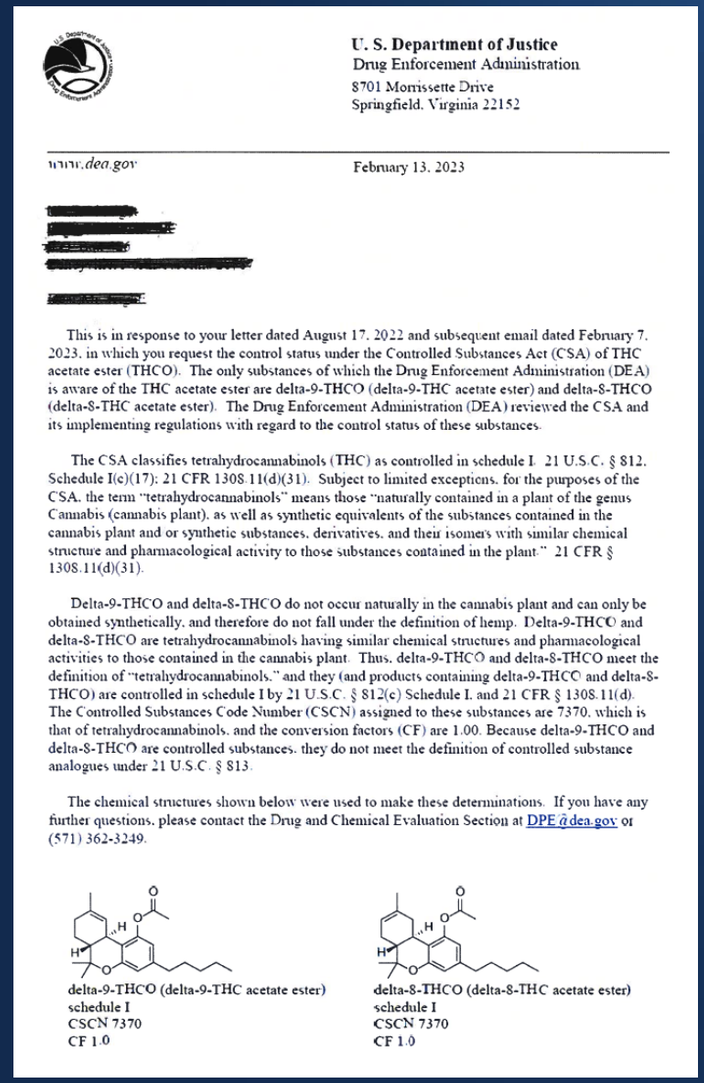
- Scientific evaluations pertaining to drug control and chemical regulations under Controlled Substances Act (CSA)
  - Control status determinations
  - Drug scheduling; chemical controls
  - Exemptions
  - Schedule I researcher registration
- Generate reports regarding drug abuse, chemical diversion, and emergent/changing drug trafficking trends
- Provide technical and regulatory control information, trends, and support to federal, state, and local public health and law enforcement officials
- Special programs to inform regulatory decisions and strategies

Control Status Inquiries

- **At anytime an entity can write into DEA (prefer email) and inquire as to the control status of a substance**
  - **Is the substance named or defined under the CSA?**
  - **Need drug codes or conversion factors?**
  - **Email box: DPE@dea.gov**
- **Include:**
  - **Chemical name**
  - **Chemical structure**
- **DEA responds by letter, copying the DEA field office**

AIA Control Status Inquiries

- Responding to inquiries related to Agricultural Improvement Act (AIA) control status
- Here to assist in complying with CSA requirements
  - Responded to over 150 control status
  - Primarily inquiries related to components of marijuana/hemp: CBD, Δ 8-THC, THCA, THCV, CBN, CBG, CBC, Δ10-THC, Δ8 and Δ 9-THCO, synthetic vs. natural, etc.
- Recent letter to law firm reaffirming tetrahydrocannabinols synthesized from non-cannabis materials are not treated as “hemp”



U. S. Department of Justice
Drug Enforcement Administration
8701 Morrissette Drive
Springfield, Virginia 22152

www.dea.gov

February 13, 2023

[redacted]

This is in response to your letter dated August 17, 2022 and subsequent email dated February 7, 2023, in which you request the control status under the Controlled Substances Act (CSA) of THC acetate ester (THCO). The only substances of which the Drug Enforcement Administration (DEA) is aware of the THC acetate ester are delta-9-THCO (delta-9-THC acetate ester) and delta-8-THCO (delta-8-THC acetate ester). The Drug Enforcement Administration (DEA) reviewed the CSA and its implementing regulations with regard to the control status of these substances.

The CSA classifies tetrahydrocannabinols (THC) as controlled in schedule I. 21 U.S.C. § 812, Schedule I(c)(17); 21 CFR 1308.11(d)(31). Subject to limited exceptions, for the purposes of the CSA, the term "tetrahydrocannabinols" means those "naturally contained in a plant of the genus Cannabis (cannabis plant), as well as synthetic equivalents of the substances contained in the cannabis plant and or synthetic substances, derivatives, and their isomers with similar chemical structure and pharmacological activity to those substances contained in the plant." 21 CFR § 1308.11(d)(31).

Delta-9-THCO and delta-8-THCO do not occur naturally in the cannabis plant and can only be obtained synthetically, and therefore do not fall under the definition of hemp. Delta-9-THCO and delta-8-THCO are tetrahydrocannabinols having similar chemical structures and pharmacological activities to those contained in the cannabis plant. Thus, delta-9-THCO and delta-8-THCO meet the definition of "tetrahydrocannabinols," and they (and products containing delta-9-THCO and delta-8-THCO) are controlled in schedule I by 21 U.S.C. § 812(c) Schedule I, and 21 CFR § 1308.11(d). The Controlled Substances Code Number (CSCN) assigned to these substances are 7370, which is that of tetrahydrocannabinols, and the conversion factors (CF) are 1.00. Because delta-9-THCO and delta-8-THCO are controlled substances, they do not meet the definition of controlled substance analogues under 21 U.S.C. § 813.

The chemical structures shown below were used to make these determinations. If you have any further questions, please contact the Drug and Chemical Evaluation Section at DPE@dea.gov or (571) 362-3249.

delta-9-THCO (delta-9-THC acetate ester)
schedule I
CSCN 7370
CF 1.0

delta-8-THCO (delta-8-THC acetate ester)
schedule I
CSCN 7370
CF 1.0

DRUG ENFORCEMENT ADMINISTRATION

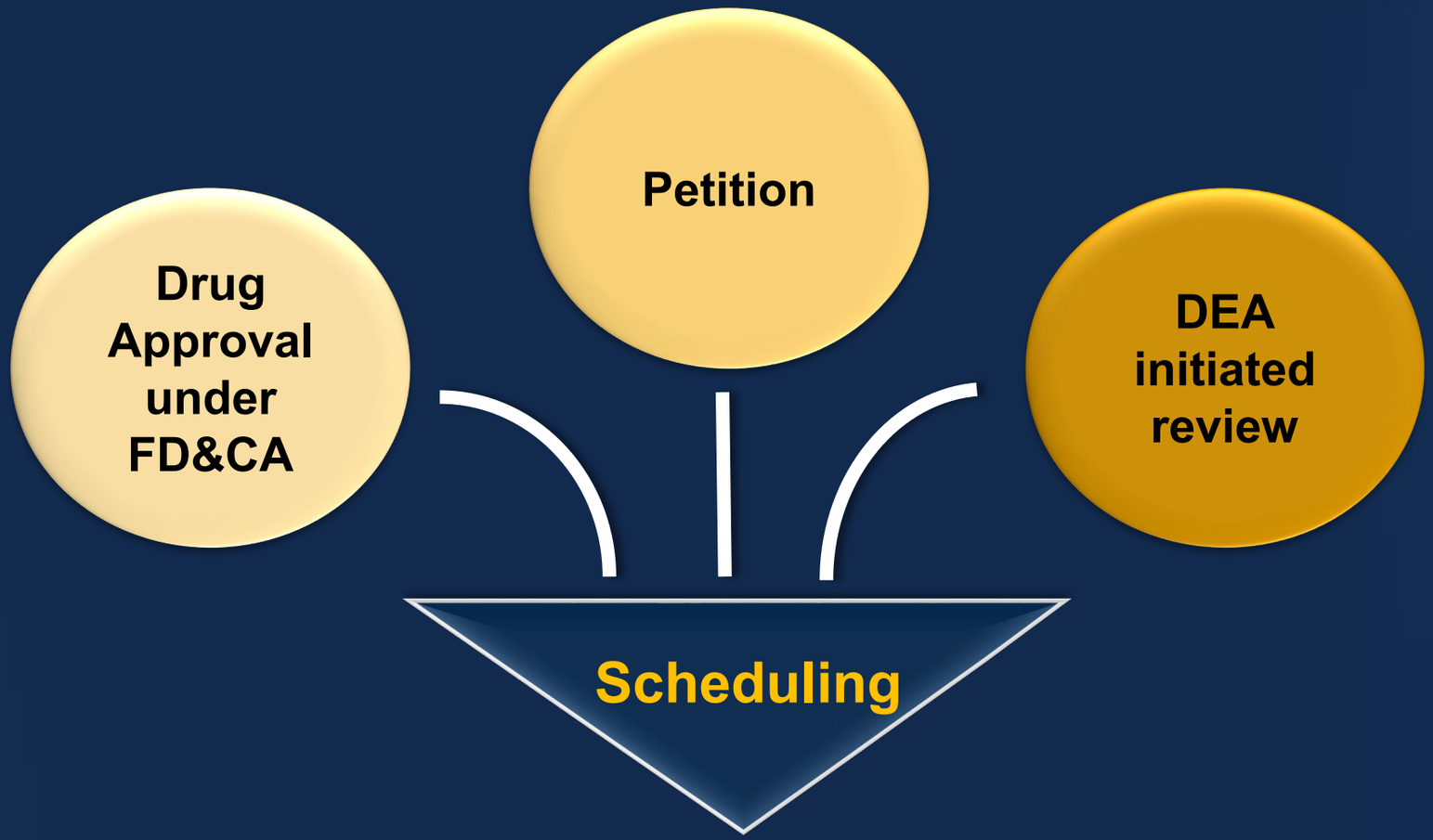
Modification of the CSA

Update Date

Control Mechanisms

- **Notice and Comment Rulemaking**
  - Substances
    - Health and Human Services (HHS) scheduling recommendation required
    - 8-Factor analysis
  - Chemicals
- **Temporary (emergency)**
  - 3 of 8 factors
  - Finding “imminent hazard to the public safety”
  - 2 years in Schedule I
- **Legislative**
  - Anabolic Steroid Control Acts of 1990, 2004, and 2014
  - Synthetic Drug Abuse and Prevention Act of 2012
- **Administrative**
  - Anabolic steroids
  - Cannabimimetic agents
- **Compliance with international treaties**

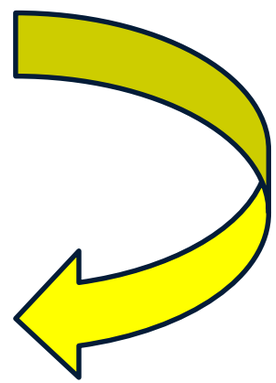
DEA Modifications to Drug Schedules



Add, Subtract, or Reschedule a substance

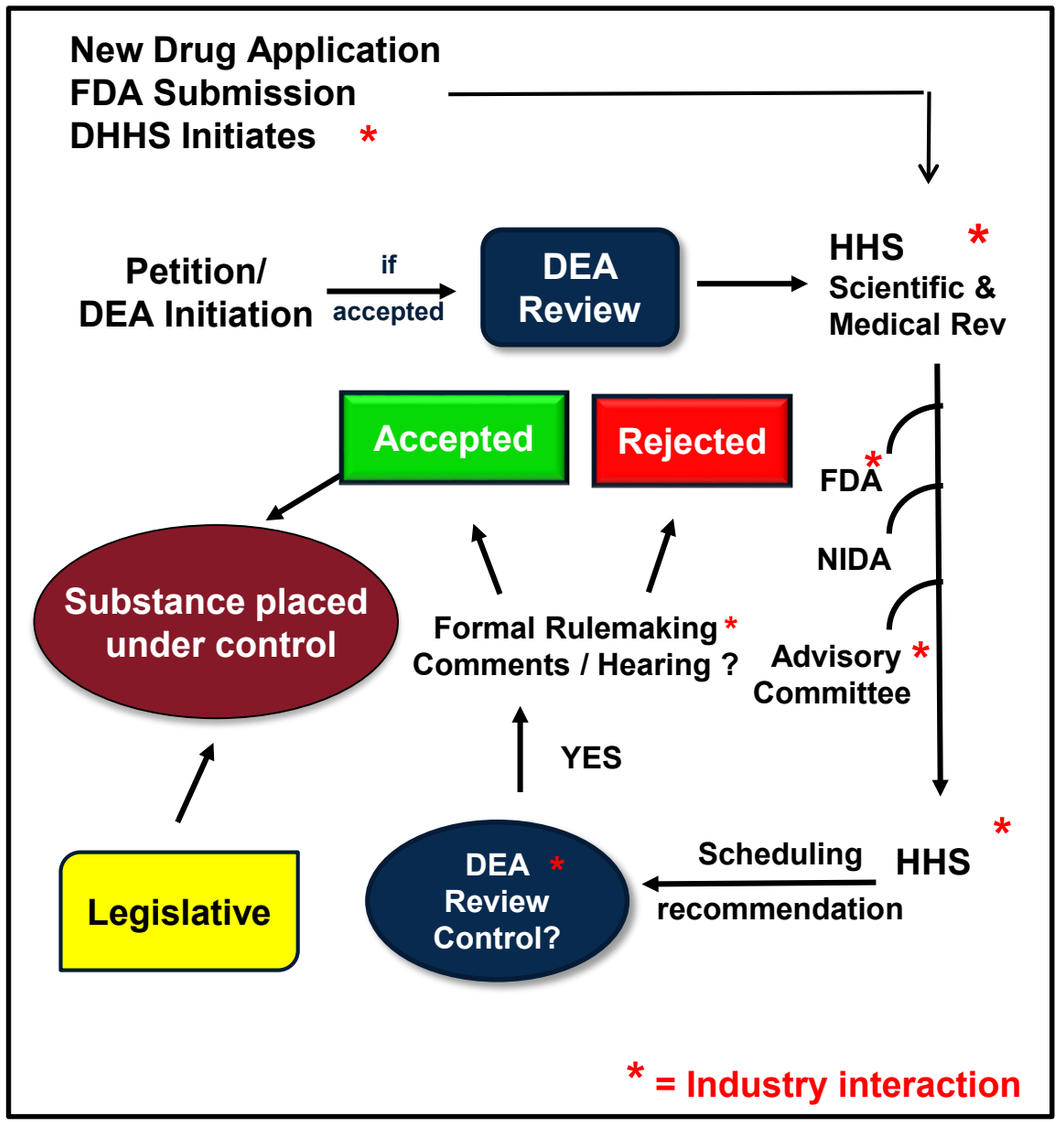
Drug Approval and Scheduling

- Defined roles for public health and law enforcement
- Food, Drug & Cosmetic Act
  - FDA requires new drugs be shown to be safe and effective for intended use before market approval
  - Approved use with abuse liability



- Controlled Substances Act
  - DEA has authority to modify
  - HHS recommendation is binding
  - Schedule I (no approved use) vs II-V placement

Scheduling Criteria and Process

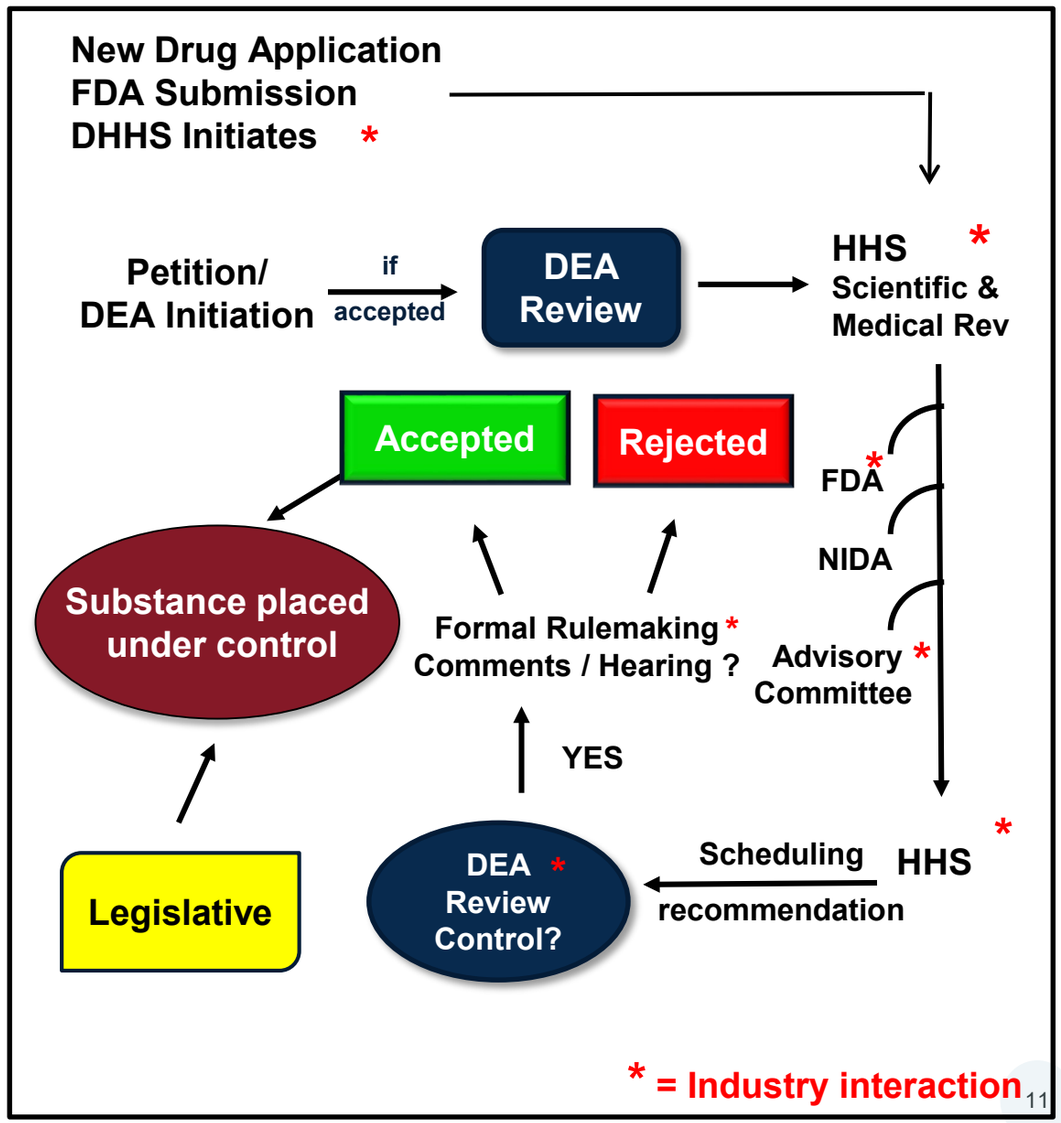


8 Factor Analysis; as set forth under 21 U.S.C 811(h), these factors are to be considered in the evaluation:

1. Its actual or relative potential for abuse
2. Scientific evidence of its pharmacological effects, if known
3. The state of current scientific knowledge regarding the drug or other substance
4. Its history and current pattern of abuse
5. The scope, duration, and significance of abuse
6. What, if any, risk there is to the public health
7. Its psychic or physiological dependence liability
8. Whether the substance is an immediate precursor of a substance already controlled

Petitions

- An entity may petition DEA to:
  - Schedule
  - Reschedule
  - Remove from schedule
- At anytime a petition can be submitted
  - If complete, DEA accepts the petition for filing and sends a letter to the petitioner
  - If incomplete, DEA sends a denial letter with an opportunity to update
- DEA conducts an 8-factor review
- Submits petition and 8-factor review to HHS for a scientific and medical review and scheduling recommendation



Exemptions under the CSA

Exclusion from some CSA requirements

- **Exclusion of Veterinary Anabolic Steroid Implant Products**
  - **(21 CFR 1308.26)**
- **Anabolic Steroid Products**
  - **(21 CFR 1308.34)**
- **Chemical Mixtures**
  - **(21 CFR 1310.12)**
- **Chemical Preparations**
  - **(21 CFR 1308.24)**
- **Prescription Drugs**
  - **(21 CFR 1308.32)**

Exemption Requests, Exceptions

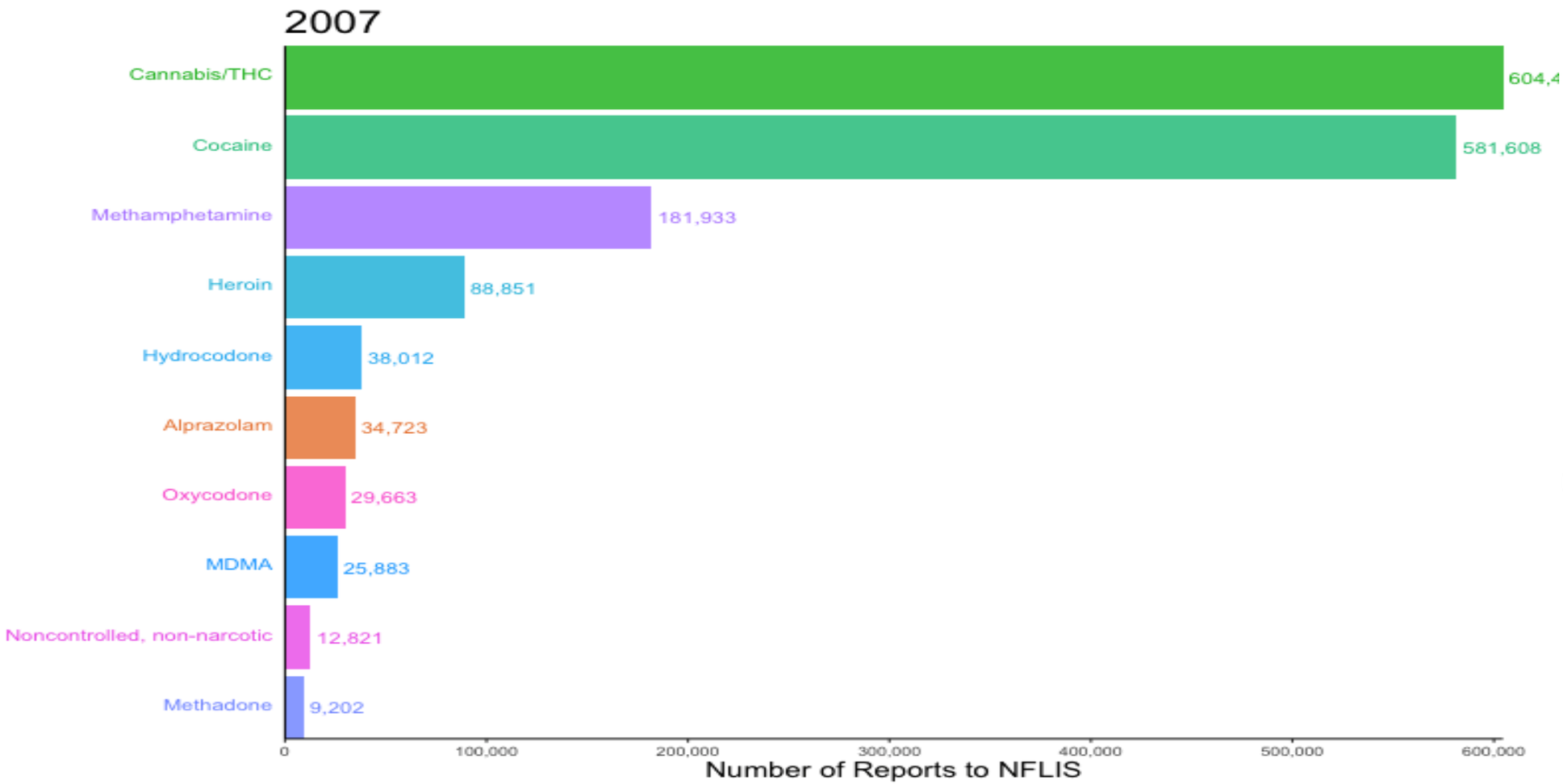
- Application process (email preferred)
- Acceptance may be required if so, a notification is provided to the requestor
- Consultation with HHS may be required with a recommendation
- Publication of exemption
- An exemption is specific to product and substance, unless otherwise noted

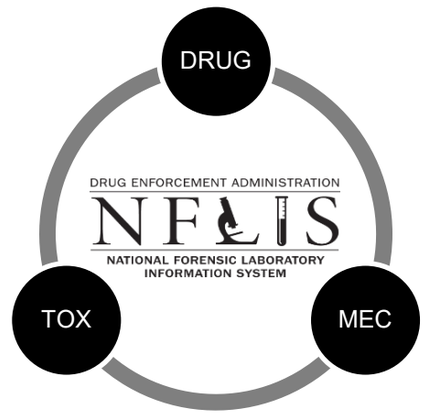
Responding and Tracking New Drugs

- Designer Drug Trending
- Scheduling Reviews
- Other Support Programs

Using NFLIS to track the U.S. Drug Situation

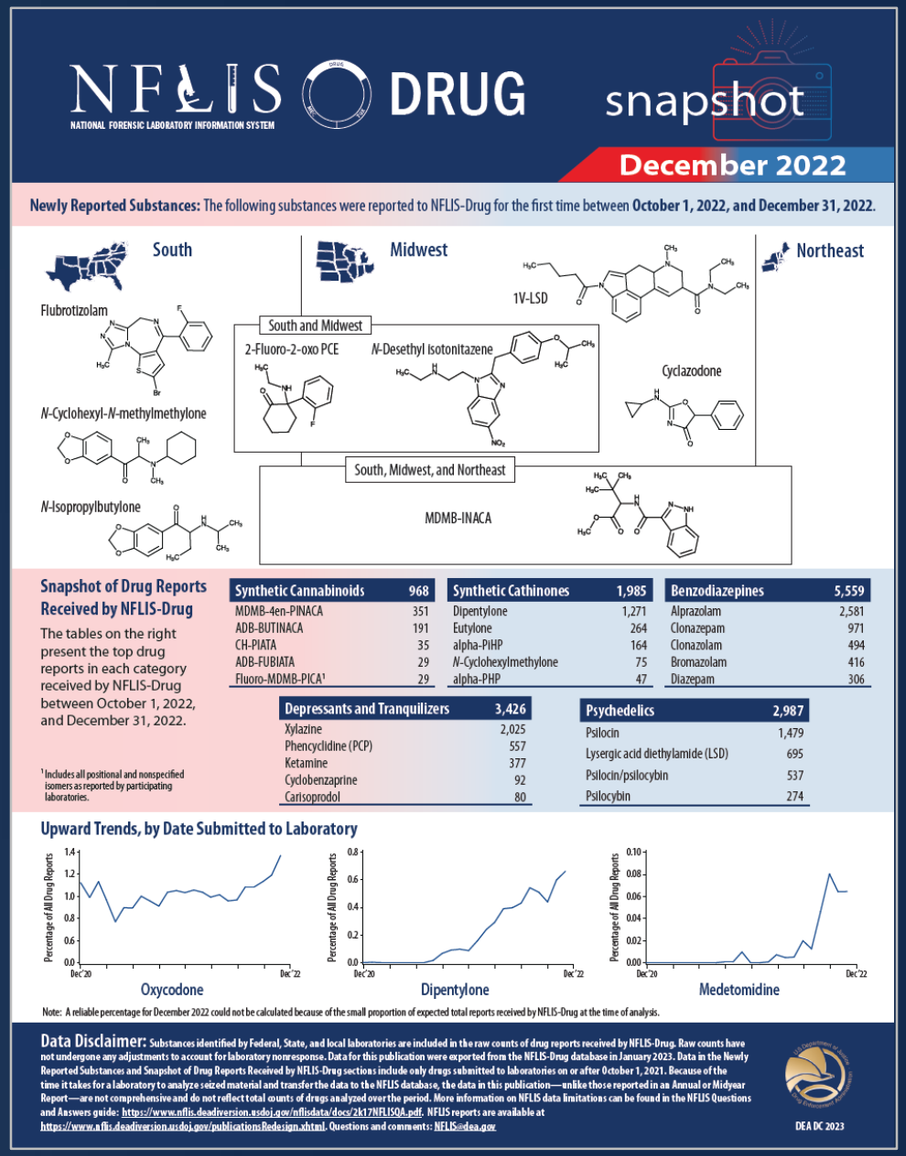
NFLIS-Drug National Estimates for the Most Frequently Identified Drugs





Source: DEA, NFLIS Public Resource Library Static Tables.
Accessed at https://www.nflis.deadiversion.usdoj.gov/Resources/NFLISPublicResourceLibrary.aspx on August 15, 2022.

Publications



NFLIS DRUG snapshot

NATIONAL FORENSIC LABORATORY INFORMATION SYSTEM

December 2022

Newly Reported Substances: The following substances were reported to NFLIS-Drug for the first time between **October 1, 2022, and December 31, 2022.**

South

Midwest

Northeast

Flubrotizolam

1V-LSD

South and Midwest

2-Fluoro-2-oxo PCE

N-Desethyl Isotonitazene

Cyclazodone

N-Cyclohexyl-*N*-methylmethylone

South, Midwest, and Northeast

N-Isopropylbutylone

MDMB-INACA

Snapshot of Drug Reports Received by NFLIS-Drug

The tables on the right present the top drug reports in each category received by NFLIS-Drug between October 1, 2022, and December 31, 2022.

[1] Includes all positional and nonspecified isomers as reported by participating laboratories.

Synthetic Cannabinoids	968
MDMB-4en-PINACA	351
ADB-BUTINACA	191
CH-PIATA	35
ADB-FUBIATA	29
Fluoro-MDMB-PICA[1]	29

Synthetic Cathinones	1,985
Dipentylone	1,271
Eutylone	264
alpha-PiHP	164
N-Cyclohexylmethylone	75
alpha-PHP	47

Benzodiazepines	5,559
Alprazolam	2,581
Clonazepam	971
Clonazolam	494
Bromazolam	416
Diazepam	306

Depressants and Tranquilizers	3,426
Xylazine	2,025
Phencyclidine (PCP)	557
Ketamine	377
Cyclobenzaprine	92
Carisoprodol	80

Psychedelics	2,987
Psilocin	1,479
Lysergic acid diethylamide (LSD)	695
Psilocin/psilocybin	537
Psilocybin	274

Upward Trends, by Date Submitted to Laboratory

Percentage of All Drug Reports

Dec '20 – Dec '22

Oxycodone

Dipentylone

Medetomidine

Note: A reliable percentage for December 2022 could not be calculated because of the small proportion of expected total reports received by NFLIS-Drug at the time of analysis.

Data Disclaimer: Substances identified by Federal, State, and local laboratories are included in the raw counts of drug reports received by NFLIS-Drug. Raw counts have not undergone any adjustments to account for laboratory nonresponse. Data for this publication were exported from the NFLIS-Drug database in January 2023. Data in the Newly Reported Substances and Snapshot of Drug Reports Received by NFLIS-Drug sections include only drugs submitted to laboratories on or after October 1, 2021. Because of the time it takes for a laboratory to analyze seized material and transfer the data to the NFLIS database, the data in this publication—unlike those reported in an Annual or Midyear Report—are not comprehensive and do not reflect total counts of drugs analyzed over the period. More information on NFLIS data limitations can be found in the NFLIS Questions and Answers guide: http://www.nflis.deadiversion.usdoj.gov/nflisdata/docs/2k17NFLISQA.pdf. NFLIS reports are available at https://www.nflis.deadiversion.usdoj.gov/publicationsRedesign.xhtml. Questions and comment:: NFLIS@dea.gov

DEA DC 2023

DEA TOX

DRUG ENFORCEMENT ADMINISTRATION

TOXICOLOGY TESTING PROGRAM

QUARTERLY REPORT

Fourth Quarter – 2022

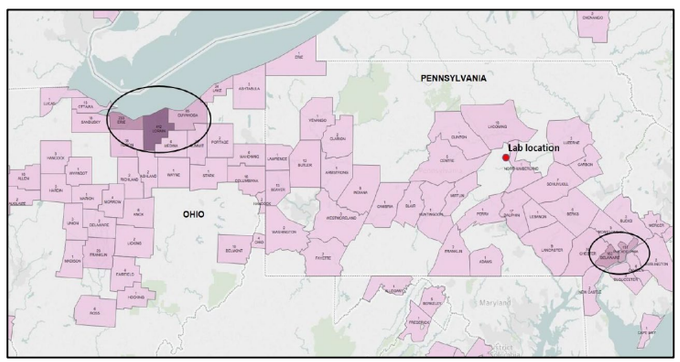
U.S. Department of Justice
Drug Enforcement Administration
Diversion Control Division
Drug and Chemical Evaluation Section

Counterfeit Pill Operations

2015 - DEA agents seized 13 kg of acetyl fentanyl along with six pill presses from a home in Los Angeles

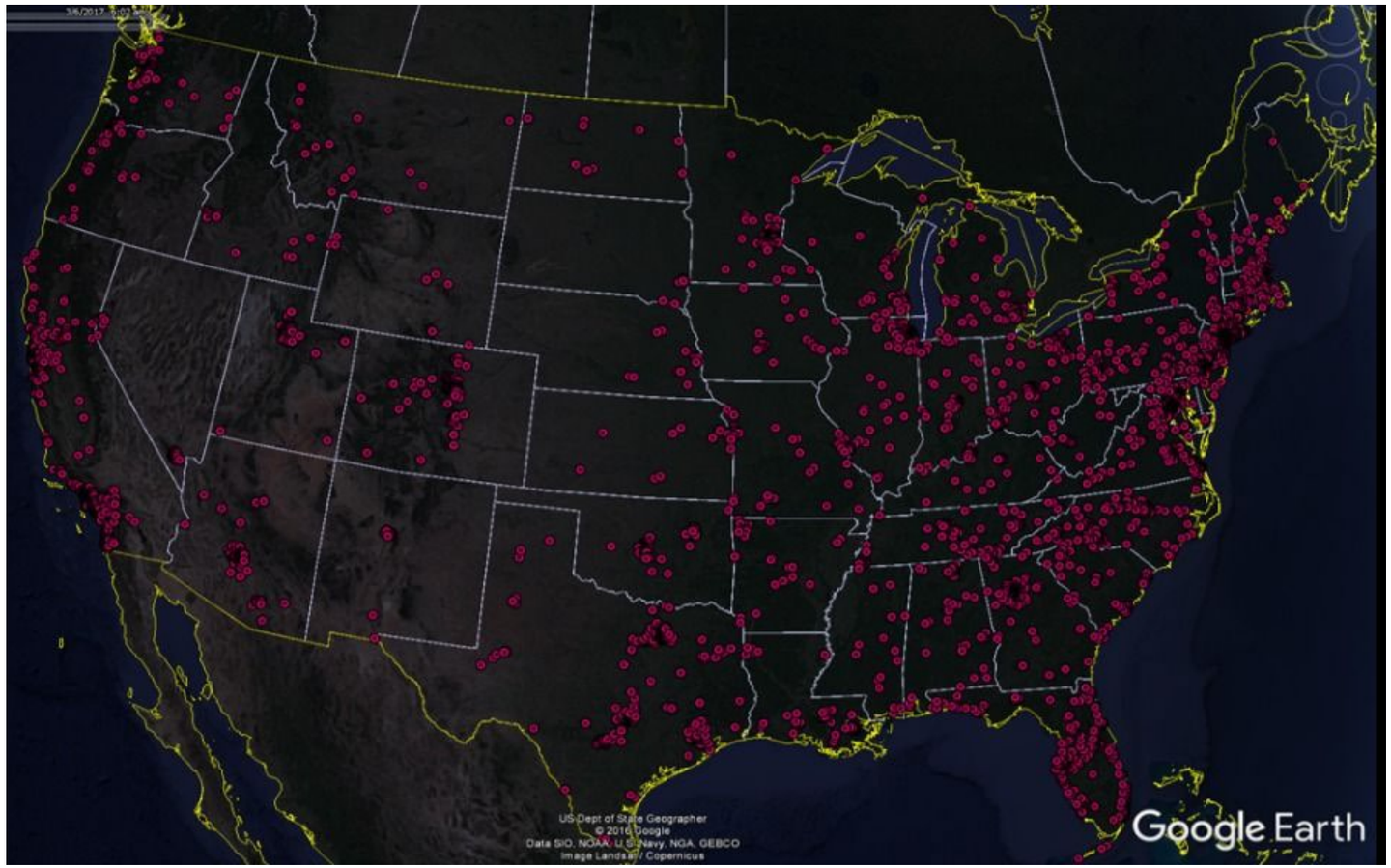
2016 - DEA responds San Francisco Norco pills various markings
14 deaths; 52 overdoses

2019 – Clandestine laboratory in Lewisburg, PA. *beta*-hydroxy-3-methylfentanyl, fentanyl, and 3-methylfentanyl
Distribution cells in PA and OH



Internet Trafficking

Pharma Master, Salt Lake City, Utah



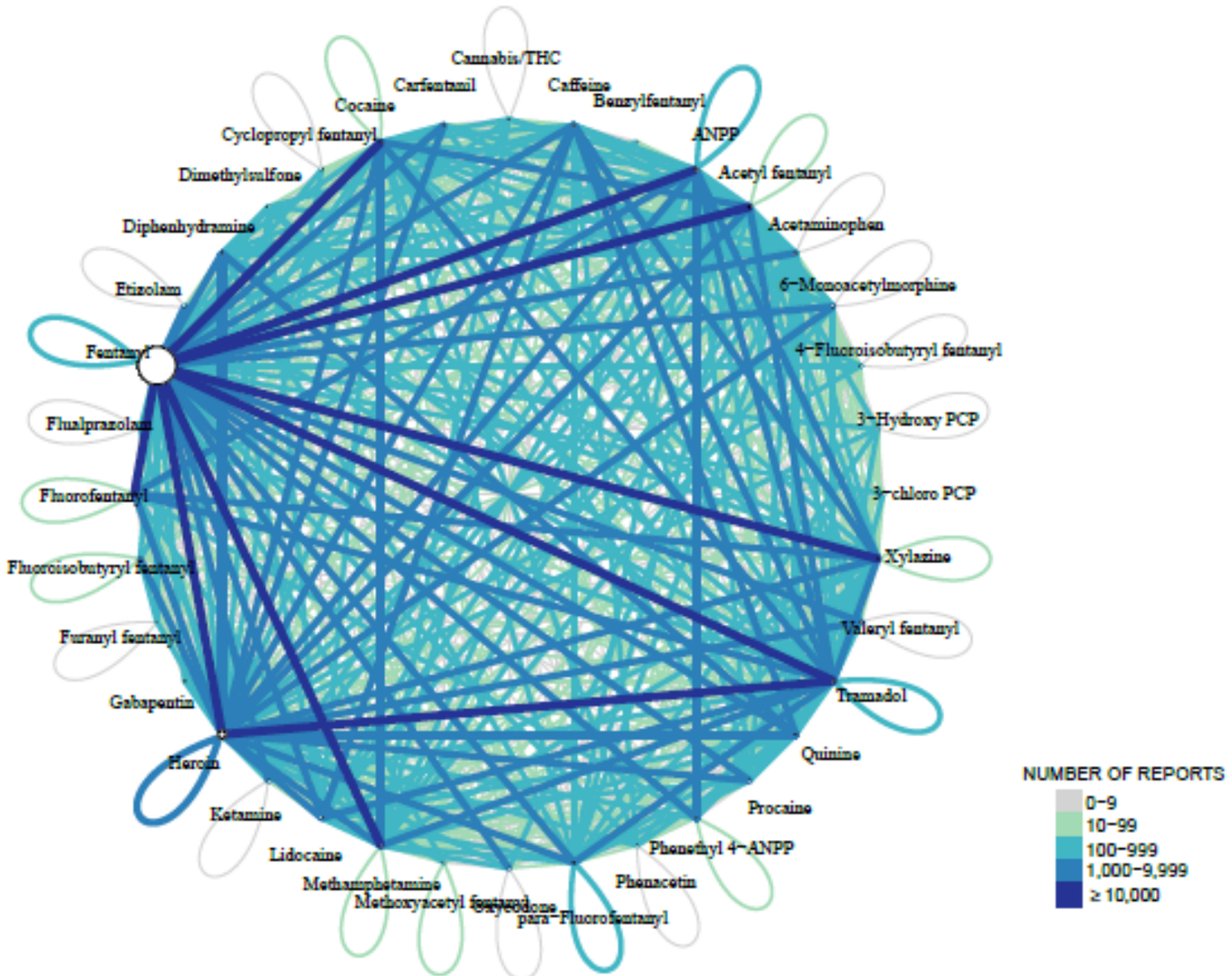
Pharma Master sales: identified zip code locations

USAUT; **Source: Desert News**

Salt Lake City, UT residence

Substances Co-Reported with Fentanyl

If the presence of illicit fentanyl alone is not bad enough - other substances are being either mixed with fentanyl or abused with fentanyl

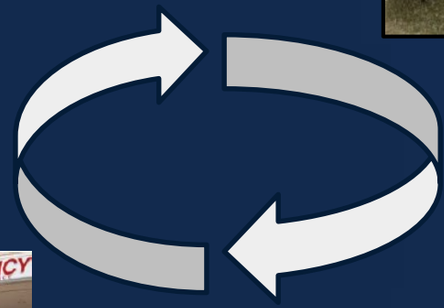


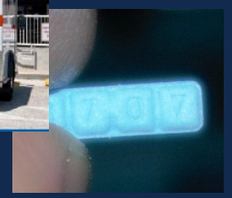
Source: DEA, NFLIS-Drug.
Accessed at https://www.nflis.deadiversion.usdoj.gov/ on October 13, 2022.

Decade of Responding to the Harm

Evolution of Designer Drugs and their Products

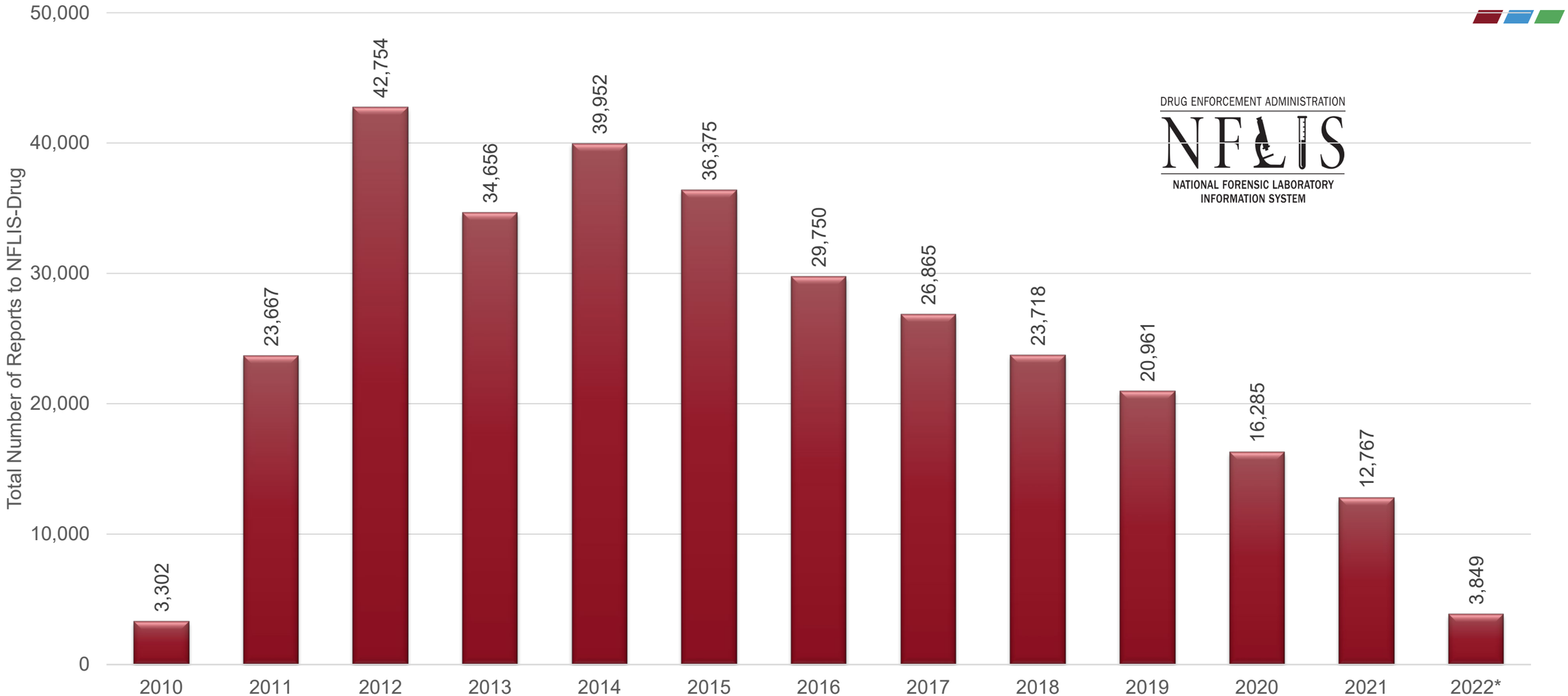
- “Spice” and “Bath Salts”
- Synthetic Cannabinoids – CBD to delta-8-THC
- Synthetic Opioids
- Designer Benzodiazepines





Death - Overland Park KS
Opioid - 2 methyl AP-237
Benzo - counterfeit Xanax (flualprazolam + clonazolam)

NFLIS-Drug: Synthetic Cannabinoid Encounters in U.S. (2010-2022*)



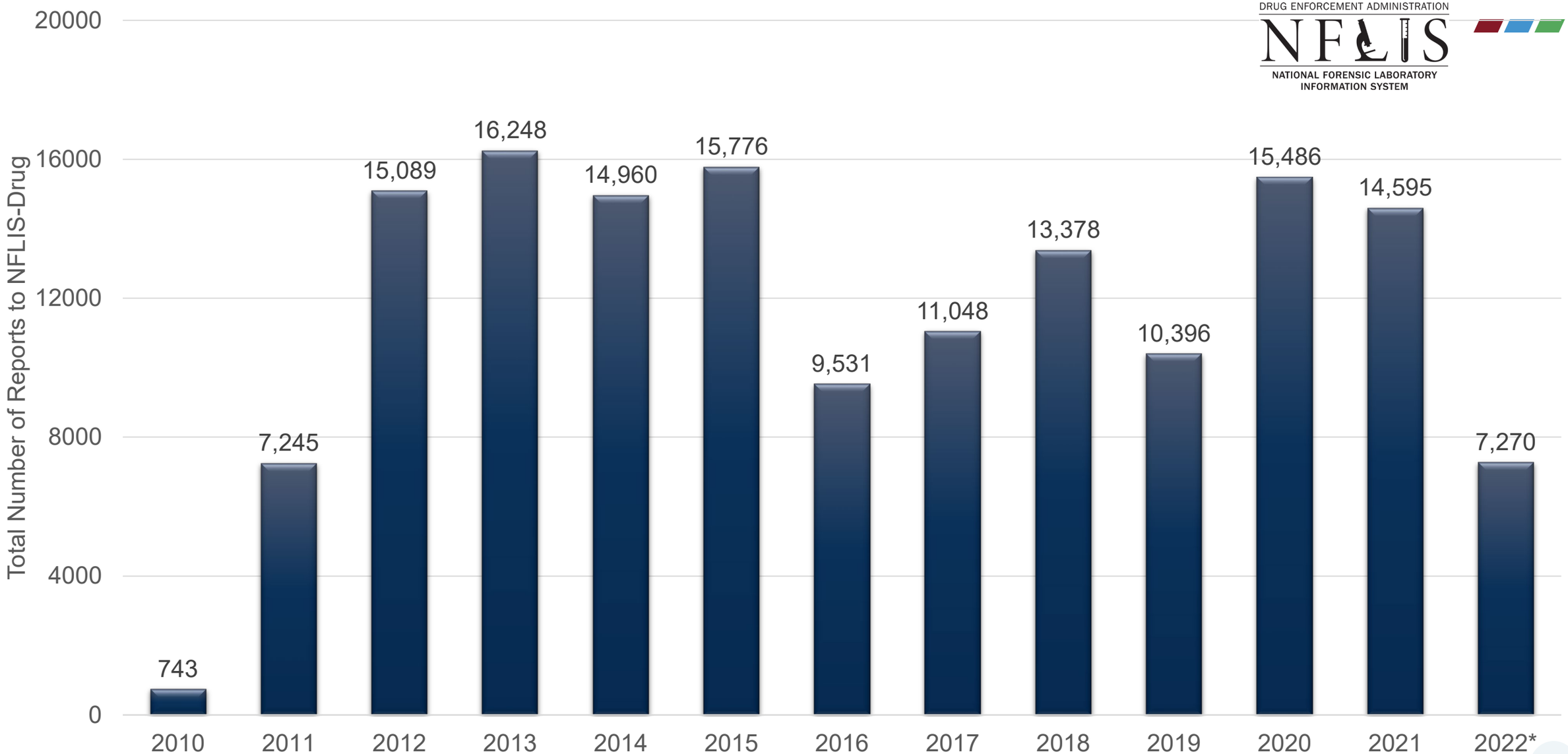
Source: DEA, NFLIS-Drug; Query date: February 9, 2023. *2022 still reporting

Synthetic Cannabinoid Controls

- Since 2011, DEA has emergency controlled 33 synthetic cannabinoids by nine emergency actions. Congress controlled 10 SC in 2012.
- Proposed rule on April 13, 2023, to consolidate 13 existing drug codes
- Emergency control proposed in April 2023:
  - MDMB-4en-PINACA
  - 4F-MDMB-BUTICA
  - ADB-4en-PINACA
  - CUMYL-PEGACLONE
  - 5F-EDMB-PICA
  - MMB-FUBICA
- SC harms still present; decline in new encounters due to China's class control

DEA-TOX:
Recent report from Baltimore probation office drug screen

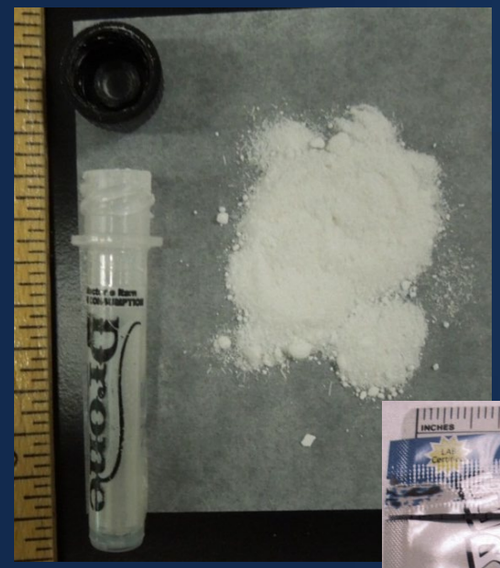
NFLIS-Drug: Synthetic Cathinone Encounters in U.S. (2010-2022*)

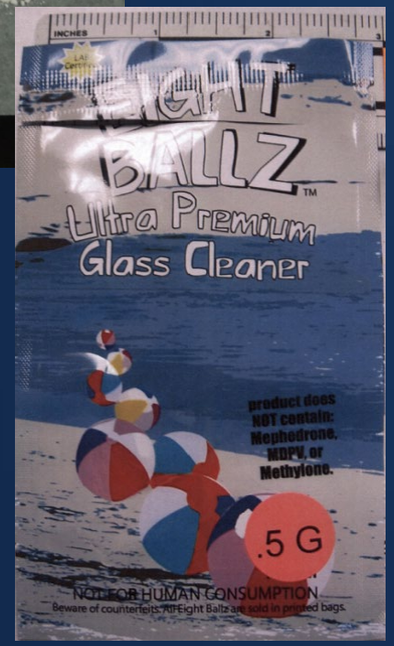


Source: NFLIS-Drug; Query date: February 14, 2023;
*2022 Still reporting

Synthetic Cathinone Trending

- Cathinone trends
  - Stable; approx. 12-15K encounters/year
  - Over 75% of all reports come from the top 5 substances in this group and the rest cover roughly 124 substances
- Data and experience suggests users have a preference for select cathinones and their associated psychostimulant high





Agricultural Improvement Act (AIA) – differential scheduling

- Exception to certain CSA requirements, noted in DEA's AIA implementation
- Subject to USDA and FDA regulations

- Required to comply with CSA
- Subject to DEA and FDA regulations

Why Overdoses = THC Percentage (<0.3% Δ9-THC dry weight)

Public Health and Safety Concerns

One impact of 2018 AIA = potent THC products

- 30 mL bottle, common retail container, could contain 81 mg of THC as noted in product analysis

- 4 g gummy, sold in 30 ct containers, could contain 12 mg of THC per gummy

THC dosage
3 mg

AIA did not define "hemp" on a w/w or w/v basis similar to drug products!

Cannabinoids and Marijuana Extracts

- CBD
  - Still waiting to finalize the AIA related rule (pending 2020)
  - Proposed rule treats synthetic CBD with <0.1% delta-9-THC same as AIA exempted material
- *delta*-8-THC
  - Very low abundance in the plant
  - CBD being converted to *delta*-8-THC by chemical step (synthesis)

Video at: https://www.nbcphiladelphia.com/news/local/montco-da-claims-fentanyl-heroin-found-in-thc-gummies/3508085

Control Status Inquiries - *delta*-8 THC

DEA response in official correspondence: "If the product contains any quantity of synthetic tetrahydrocannabinol, it is controlled in schedule I of the CSA, unless it is specifically excepted or listed in another schedule The Agricultural Improvement Act of 2018 (AIA), Pub. L. 115-334, § 12619, amended the CSA to remove"

(From testimony by Steven Crowley on Oregon HB 3000, 03/25/2021)

consumers may have a false sense of safety and legality, as *delta*-8 THC products may be labeled as "hemp", which consumers may not associate with psychoactive ingredients and negative outcomes

Challenge for forensic labs and regulators

Delta 8 THC Vape Cartridge

Source of *delta*-8 THC

Where did come from?

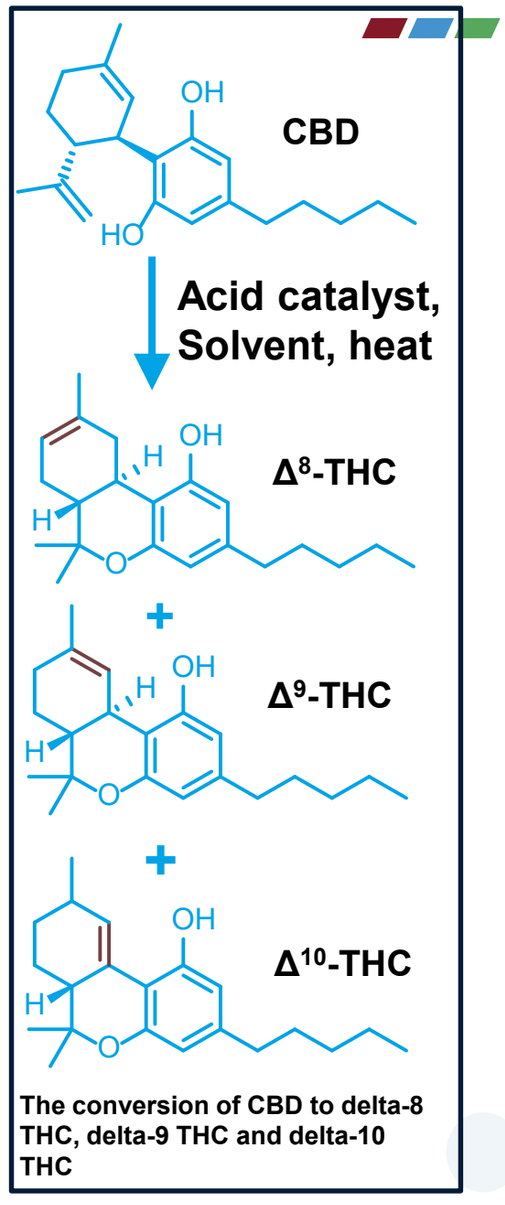
or

?

"Whether a cannabinoid product that has been synthetically produced from non-cannabis materials is controlled depends on whether that product contains "any quantity" of a synthetically produced tetrahydrocannabinol. See 21 U.S.C. 812, Schedule I(c)(17); 21 CFR 1308.11(d)(31); see also Implementation of the Agriculture Improvement Act of 2018, 85 FR 51639, 51641 (2020). This includes cannabinoid products that are chemically identical to cannabinoids that naturally occur in the cannabis plant but that have been manufactured synthetically rather that produced by extraction from the plant."

Online recipe

1. **Extract CBD from hemp.** You can learn about CBD extraction in our *From Seed To Sale: How CBD Oil Is Made*
2. **Dissolve the CBD.** A solvent is combined with the CBD extract to separate out its parts.
3. **Add an acid.** An acid is incorporated into the solution, which is then heated and mixed for up to 18 hours.(1) This causes a chemical reaction that rearranges the molecules to form a substance that contains delta-8 and delta-9.
4. **Neutralize the acid.** This balances out the acid from the previous step.
5. **Clean it up.** The new substance needs to be washed to remove remaining traces of the acid and solvent used in the chemical reactions.
6. **Distill the new substance.** This further purifies and isolates the D8 and D9.
7. **Dilute or remove the D9.** While the final distillate is mostly delta-8 (60-70%), it also contains about 2-6% delta-9-THC.(2) Processors will refine the distillate to the target D8/D9 levels (e.g., to make it fall within legal THC limits).
8. **Test for potency and contents.**The final delta-8-THC is analyzed to determine or confirm the amount of delta-8 (and other cannabinoids) it contains. Testing will also reveal any other substances — residue from processing compounds, pesticides, etc. — riding the D8 coattails.



The conversion of CBD to delta-8 THC, delta-9 THC and delta-10 THC

- **If a synthetic tetrahydrocannabinol = CI controlled substance**
- **DOE does not comment or respond to private lab analyses**

delta-8 THC

Another patchwork of laws at the state and local level

States that have banned *delta*-8 THC

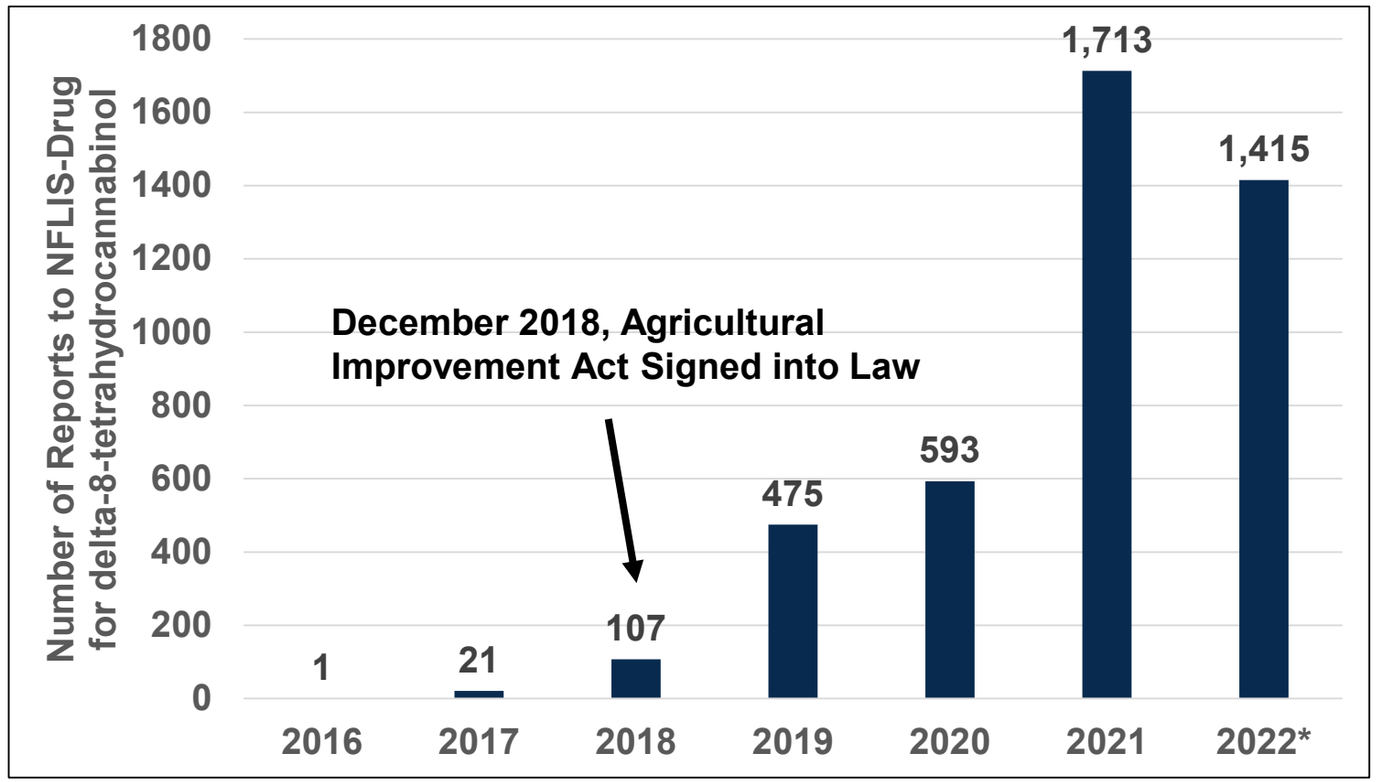
Alaska	Nevada
Colorado	North Dakota
Delaware	Oregon
Idaho	Rhode Island
Iowa	Utah
Montana	Vermont
New York	Washington

States that regulate *delta*-8 THC sales

Connecticut	Michigan

Some other states have other laws that could potentially affect *delta*-8-tetrahydrocannabinol, like the use of inhalable products being banned

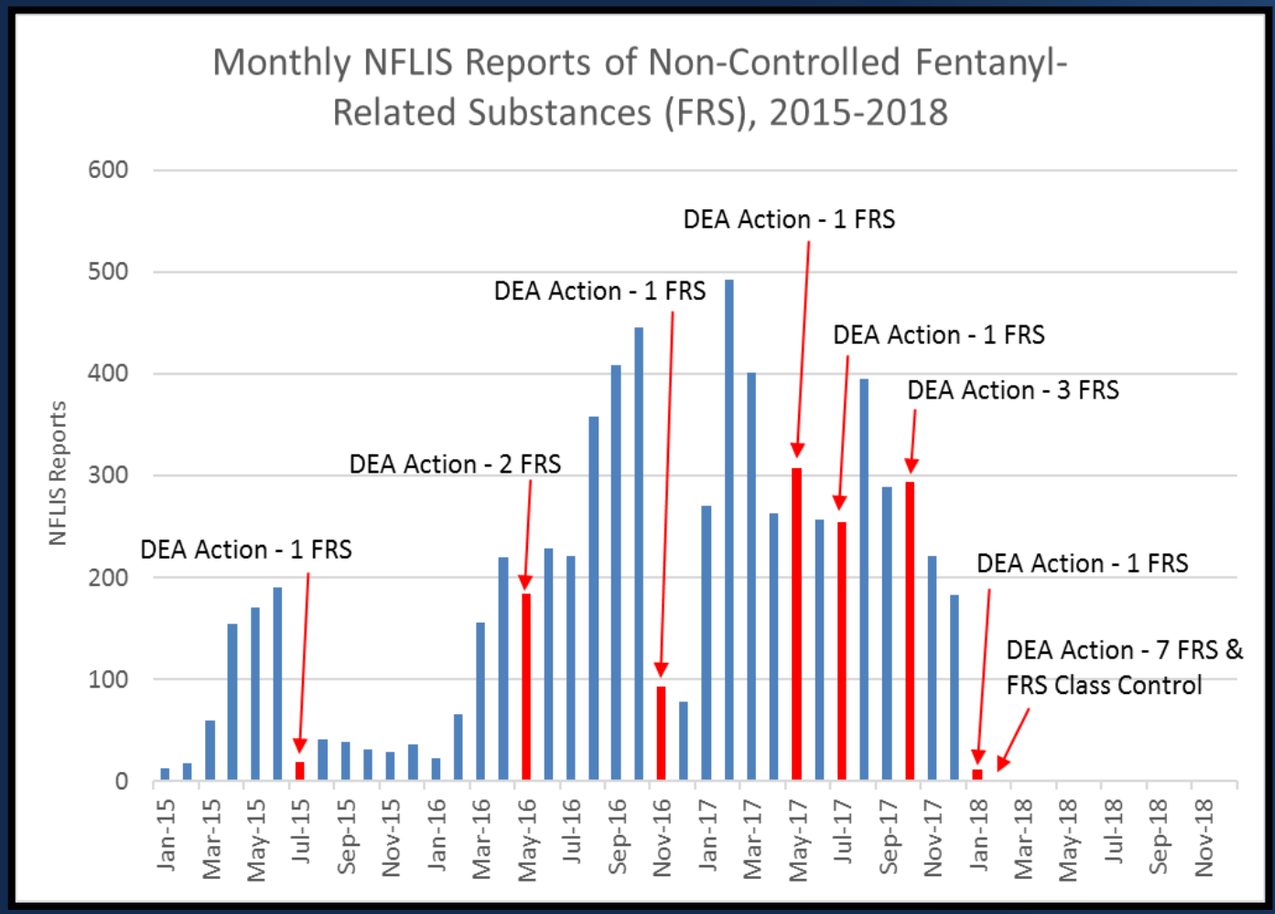
delta-8 THC Reporting to NFLIS



NFLIS-Drug queried February 27, 2023; *2022 still reporting

Fentanyl-Related Substances

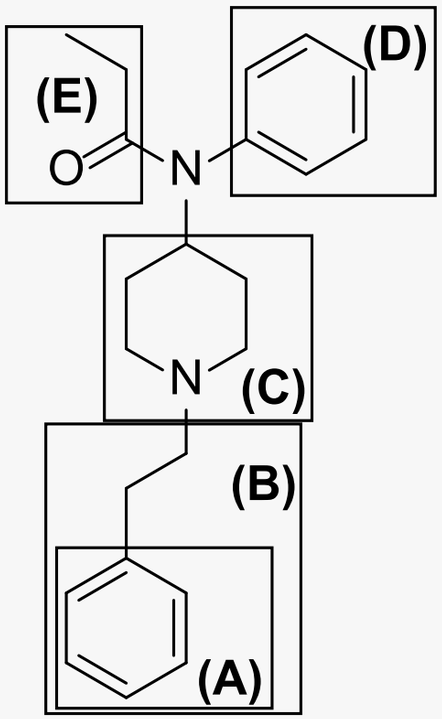
- China played a significant role as source country and also critical to correcting
- Initiating Controls
  - Multiple emergency control actions – every few months
  - DEA issues class control - Feb 2018
  - China issues class control - May 2019
- Congress extends temporary class control
  - Latest extension expires on Dec 31, 2024



- 2021 USSC modified fentanyl analog definition

Behind the Scenes

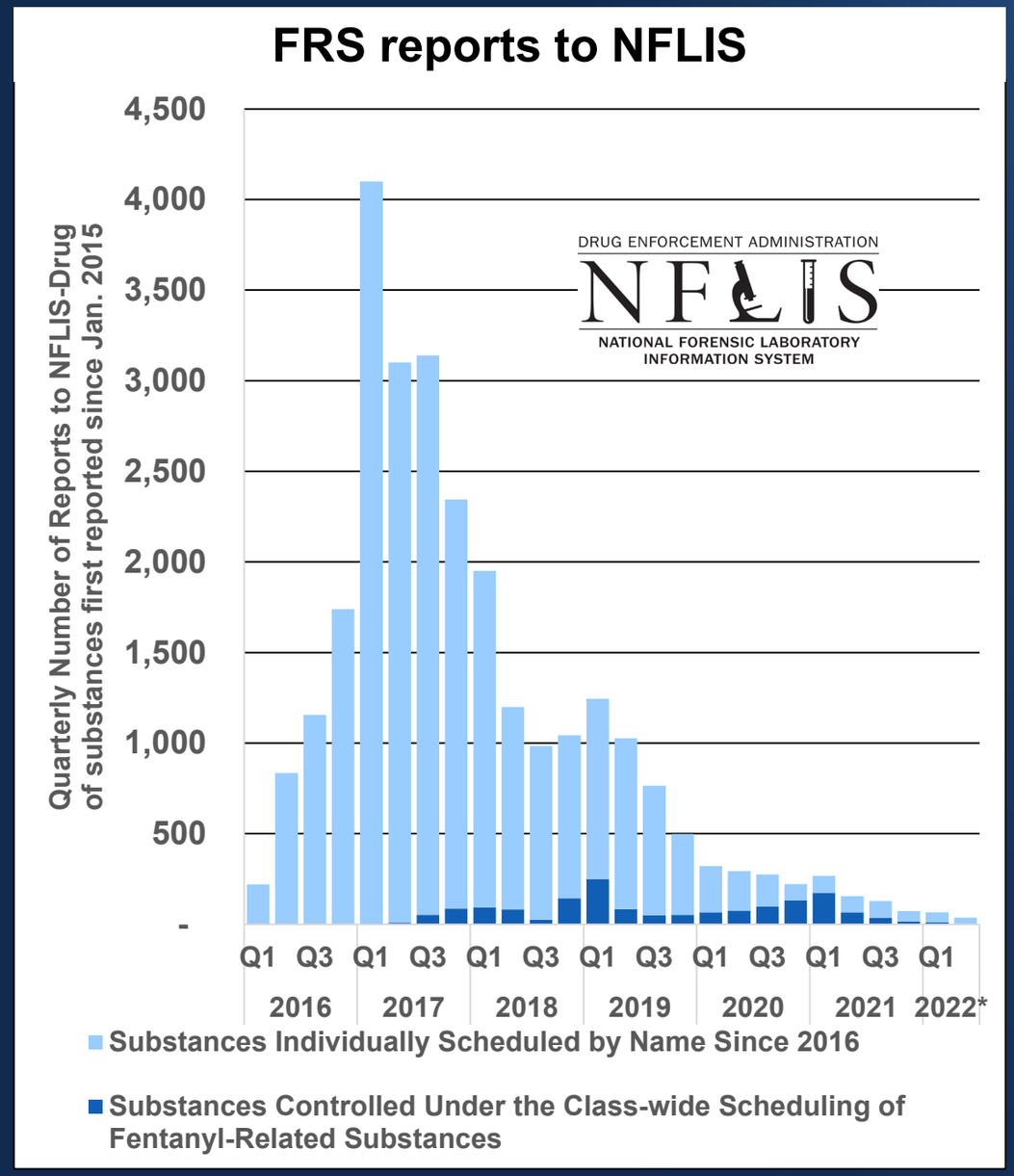
- Support providing factual evidence to Congress to inform the discussion
- Working to permanently control all encountered FRS
  - Collecting encounter, harm info
  - DEA pharmacology testing
- HHS provides a scientific and medical evaluation and scheduling recommendation
  - Recommended control 9 - May 2022
  - Letter to HHS for additional 7 FRS - sent
- WHO consideration for control under the 1961 Single Convention



FRS Structural Definition

Effect of Class Control

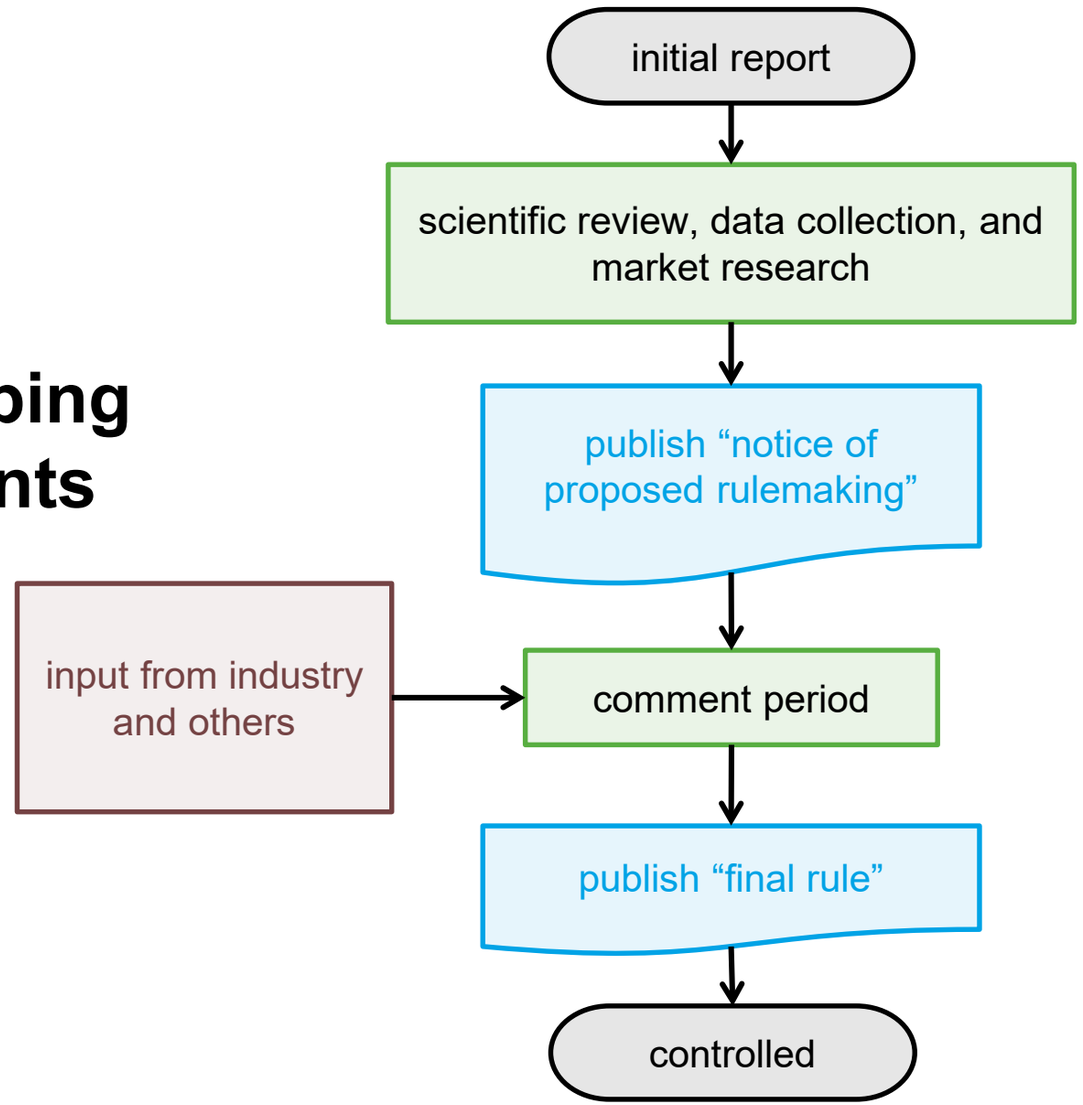
- **Class control has been closely examined - GAO audit**
- **Stats**
  - *How many FRS have been encountered to date?* **36**
  - *Last new FRS encountered?* **February 2022**
  - *How many FRS have been placed under permanent control?* **20**
  - *How many FRS pending permanent control?* **16**



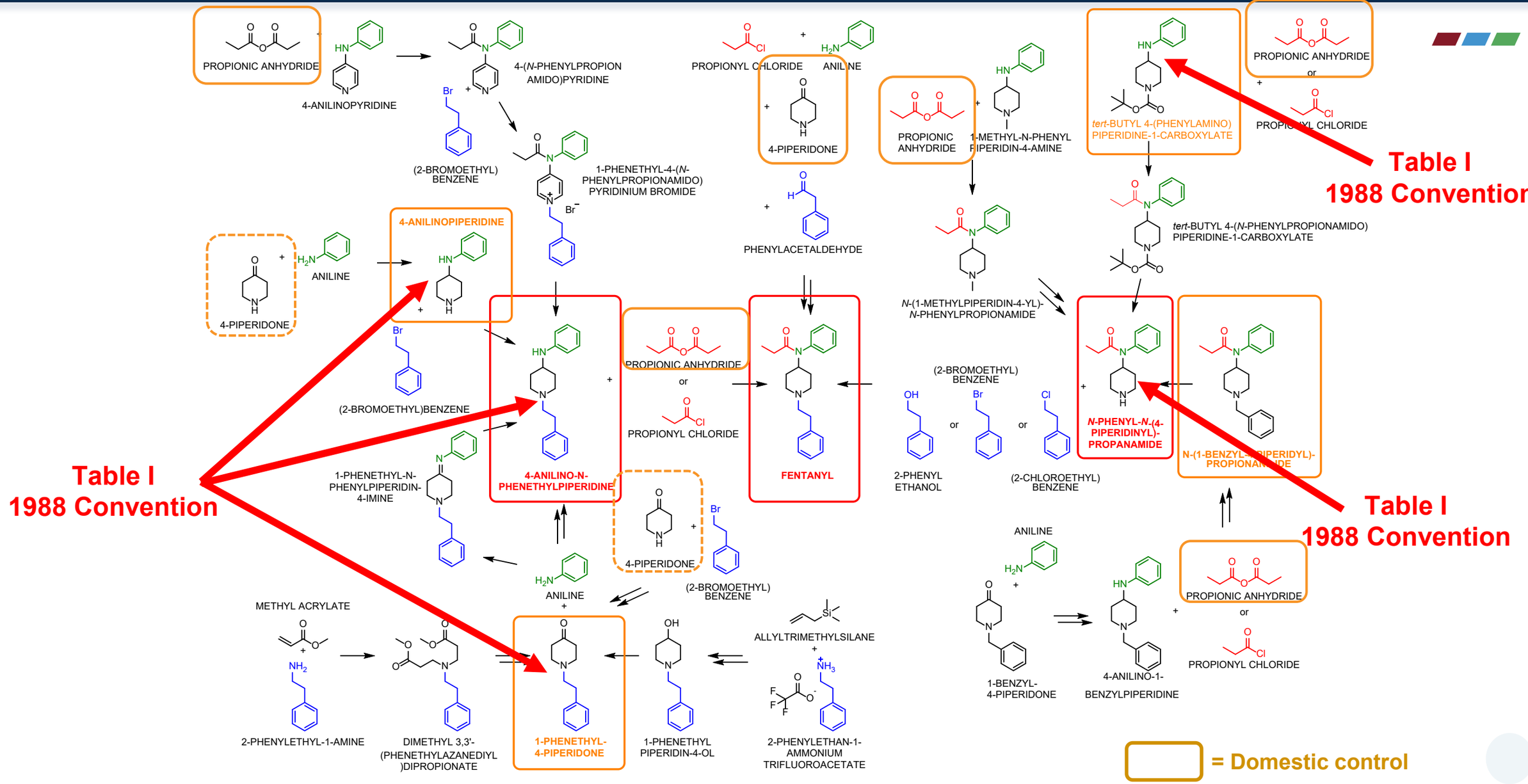
Source: DEA, National Forensic Laboratory Information System (NFLIS-Drug), queried on August 15, 2022. Data excludes substances controlled prior to 2016.
*Reports still pending for 2022.

Enacting a New Chemical Control

- **Authority delegated to DEA**
- **If finalized:**
  - **Registration, record keeping and reporting requirements for manufacture, distribution, importation, and exportation**
  - **Requirement to know customer and report suspicious orders**



Precursors Involved in Fentanyl Synthesis

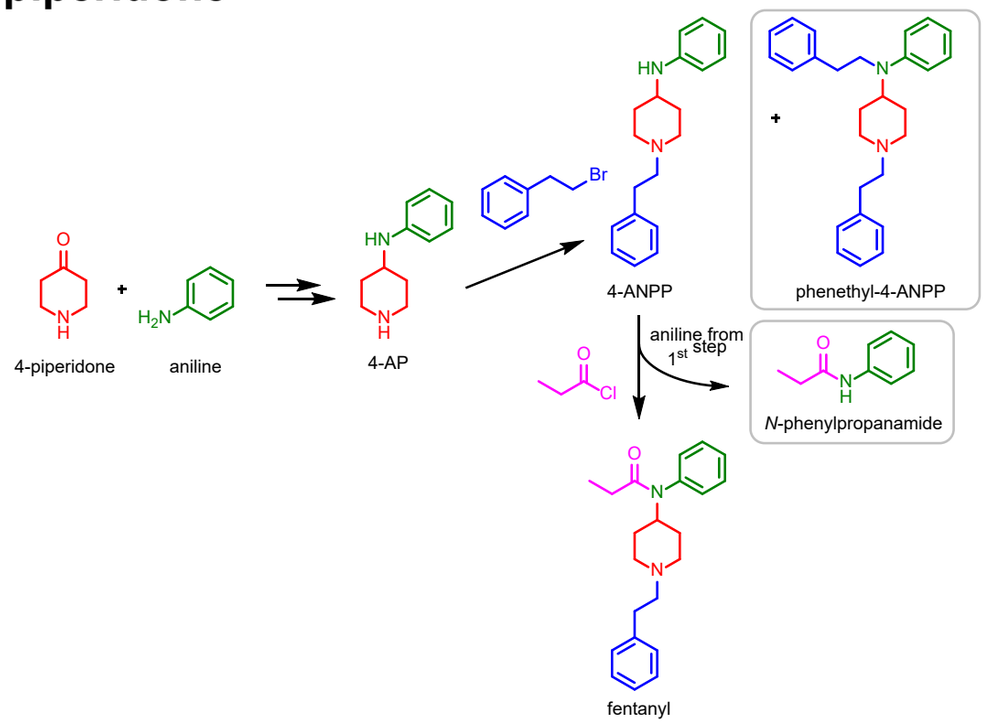


Information: Key to Prioritizing

- **Re-engineering seizure information**
  - **Shipment labels**
  - **Laboratory findings**
  - **Impurity profiles**
- **Knowing the chemical needs of industry and engaging industry to know their customers**

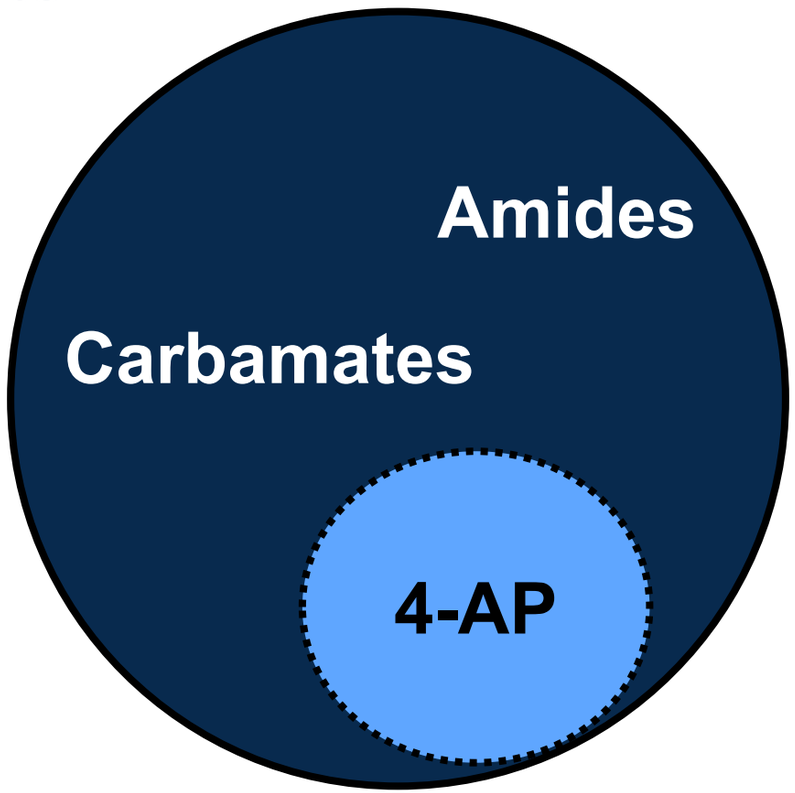
Example:
Fake M30 pill: containing acetaminophen, dipyrone, dimethyl sulfone, fentanyl, noramidopyrine, phenethyl 4-ANPP, 4-ANPP, ET ANPP and N-phenylpropanamide

Info tells us: clandestine method is starting with 4-piperidone



2020 Chemical Control

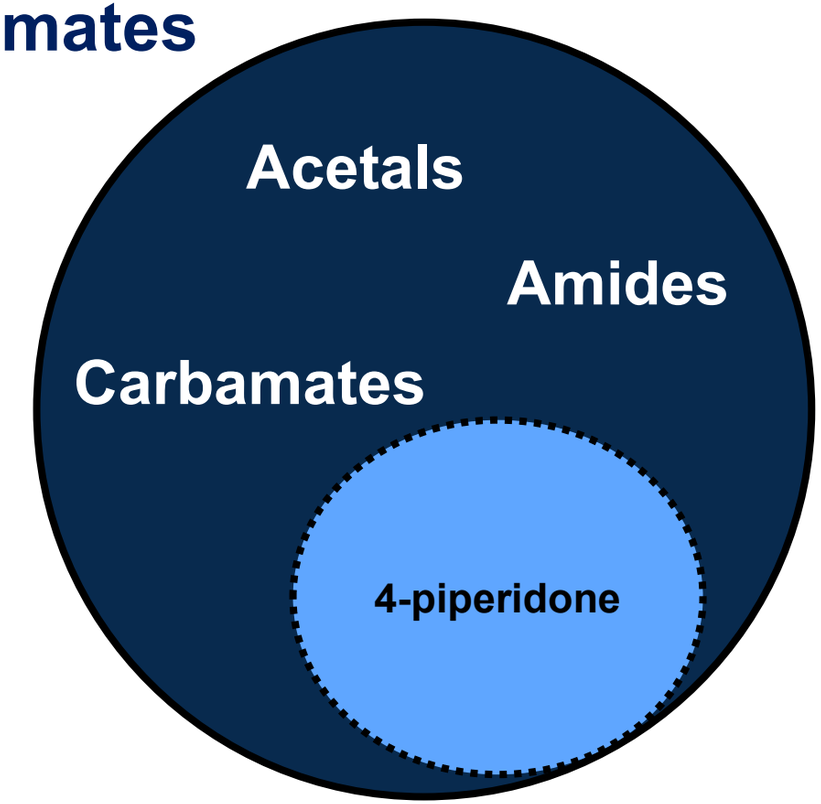
- **4-Anilinopiperidine (4-AP), its amides, its carbamates, and its salts**



- **Controlled and encountered to date:**
  - **4-AP**
  - **1-boc-4-AP**
  - **acetyl norfentanyl**
  - **ethyl 4-anilinopiperidine-1-carboxylate**
  - **furanyl norfentanyl**
  - **butyryl norfentanyl**
  - **cyclopropyl norfentanyl**
  - **valeryl norfentanyl**
  - **isobutyryl norfentanyl**
  - **1-Cbz-4-AP**
- **April 2023: published proposed rule to include halides of 4-AP to list 1 chemicals**

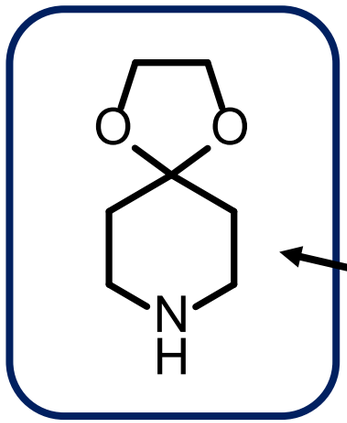
April 2023 Control

- 4-Piperidone, its acetals, its amides, its carbamates, its salts, and salts of its acetals, its amides, and its carbamates

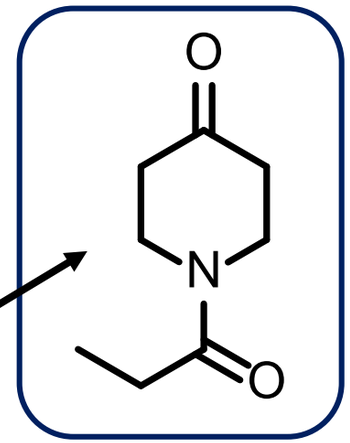


- Controlled:
  - 4-piperidone
  - definition includes:
    - 1-boc-4-piperidone
    - 1-Cbz-4-piperidone
    - 1-propionyl-4-piperidone
    - 4-piperidone ethylene ketal

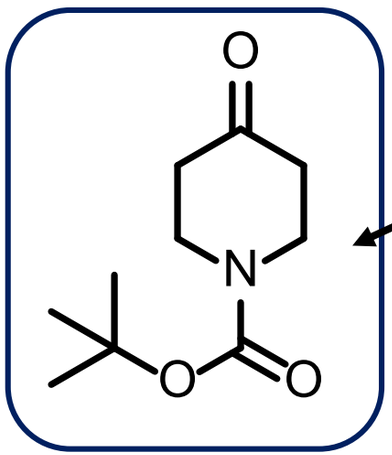
What is captured under List I …..



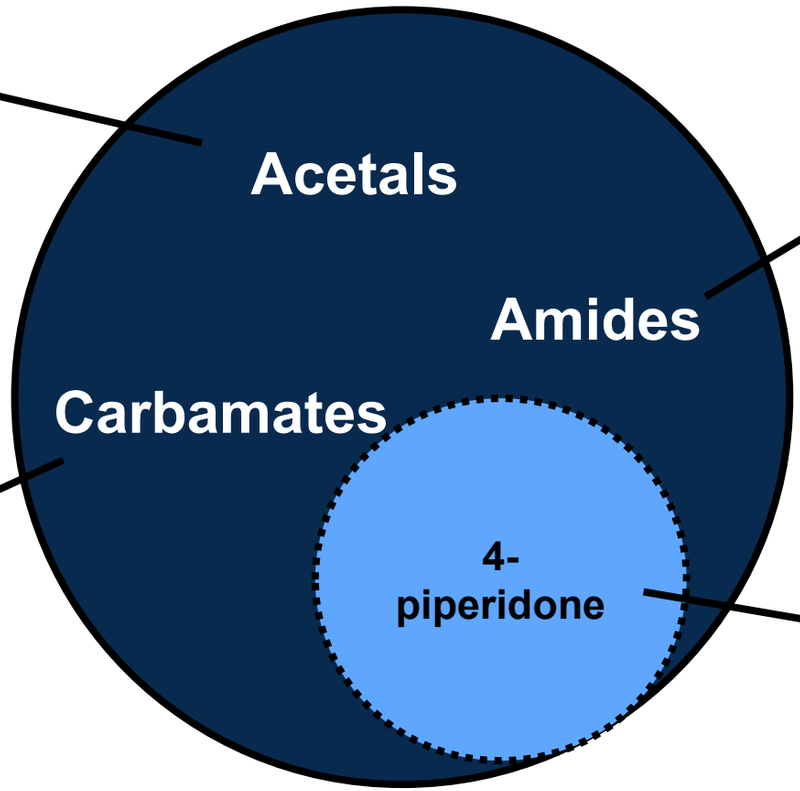
4-piperidone ethylene ketal

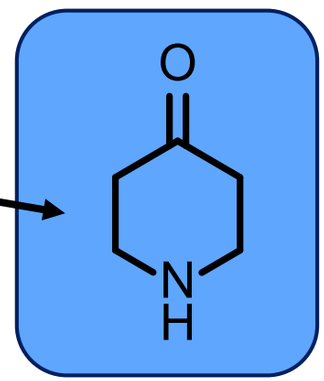


1-propionyl-4-piperidone



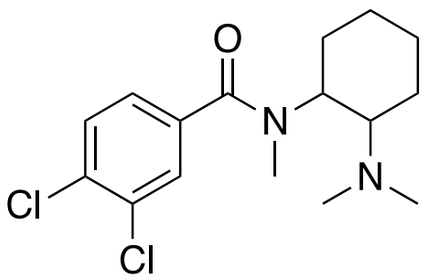
1-boc-4-piperidone



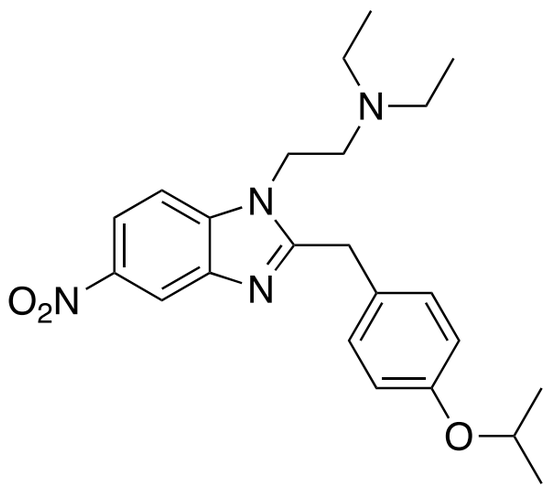


Appearance of New Synthetic Opioids

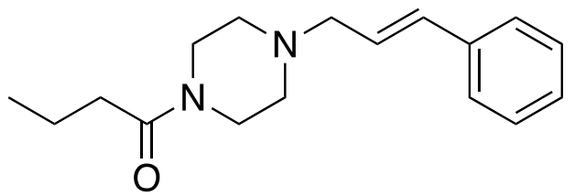
How does control of fentanyl and fentanyl analogues change the drug landscape?
……Emergence of new synthetic opioids - all potent opioids and evade controls……



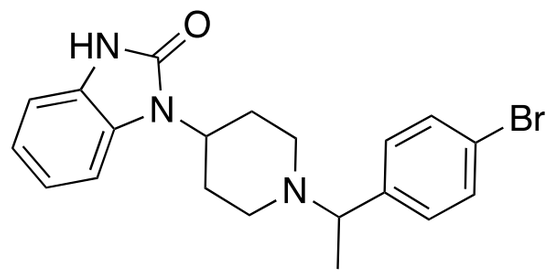
U-Series



Benzimidazoles



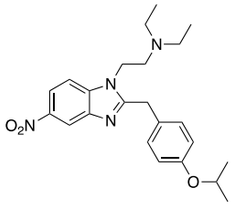
AP Series



Misc.

Benzimidazole-Opioids – Analgesic Potency Comparison

- Prioritize the most <u>prevalent, persistent, and harmful</u> of substances for domestic and international control
- DEA contract studies (sharing study reports via UNODC Toolkit)
  - Receptor binding and functional studies to determine opioid agonist profile
  - Analgesia studies to determine effect and potency
  - Behavioral pharmacology studies to access abuse potential
- Preliminary findings:
  - All benzimidazoles (aka “nitazenes”) are opioid agonists
  - Effects reversed by antagonist (naltrexone)
  - Provide initial estimates as to analgesic potency



Benzimidazole-opioids

Substance	Encounter	*In Vitro*		*In Vivo*		Control Status		HHS Request
	Type of report	Binding at MOR (Ki)	Function at MOR (Effect/EC_{50})	Analgesic Activity (ED_{50})	Morphine Drug Discrimination (ED_{50})	United States	International	Date DEA transmitted
Butonitazene	NFLIS; Tox	1.05 nM	Full Agonist (3.4 nM)	Analgesia (0.96 mg/kg)	Full Substitution (0.42 mg/kg)	Temporary control Apr 2022		Sent Jul 2022
Etodesnitazene	NFLIS; Tox	0.316 nM	Full Agonist (42 nM)	Analgesia (0.052 mg/kg)	Full Substitution (0.018 mg/kg)	Temporary control Apr 2022	*Pending, Mar 2023 CND*	Sent Jul 2022
Flunitazene	NFLIS; Tox	3.63 nM	Full Agonist (259 nM)	Analgesia (38.4 mg/kg)	Full Substitution (2.5 mg/kg)	Temporary control Apr 2022		Sent Jul 2022
Isotonitazene	NFLIS; Tox	0.323 nM	Full Agonist (0.381 nM)	Analgesia (0.0025 mg/kg)	Full Substitution (0.0033 mg/kg)	Temporary control 2020; Permanent control Nov 2021	Yes 2021 CND	No requirement controlled internationally
Metodesnitazene	NFLIS; Tox	9.3 nM	Full Agonist (1200 nM)	Analgesia (3.3 mg/kg)	Full Substitution (0.92 mg/kg)	Temporary control Apr 2022		Sent Jul 2022
Metonitazene	NFLIS; Tox	0.20 nM	Full Agonist (7.5 nM)	Analgesia (0.2 mg/kg)	Full Substitution (0.012 mg/kg)	Temporary control Apr 2022; *Permanent control pending*	Yes 2022 CND	No requirement controlled internationally
5-Methyl etodesnitazene	None	1.94 nM	Full Agonist (5.0 nM)	*Pending*	*Pending*			
N-Desethyl isotonitazene	NFLIS;Tox	0.109 nM	Full Agonist (0.093 nM)	*Pending*	*Pending*			*Pending since Jan 2023*
N-Piperidinyl etonitazene	Tox	0.120 nM	Full Agonist (2.37 nM)	*Pending*	*Pending*			*Pending since Jan 2023*
N-Piperidinyl isotonitazene	None	0.43 nM	Full Agonist (0.63 nM)	*Pending*	*Pending*			
N-Pyrrolidino etonitazene	NFLIS; Tox	0.161 nM	Full Agonist (1.68 nM)	Analgesia (0.0017 mg/kg)	Full Substitution (0.00080 mg/kg)	Temporary control Apr 2022	*Pending, Mar 2023 CND*	Sent Jul 2022
N-Pyrrolidino isotonitazene	None	0.68 nM	Full Agonist (0.233 nM)	*Pending*	*Pending*			
N-Pyrrolidino metonitazene	None	1.51 nM	Full Agonist (17.5 nM)	*Pending*	*Pending*			
N-Pyrrolidino protonitazene	None	0.286 nM	Full Agonist (0.35 nM)	*Pending*	*Pending*			
Protonitazene	NFLIS; Tox	0.216 nM	Full Agonist (4.7 nM)	Analgesia (0.035 mg/kg)	Full Substitution (0.008 mg/kg)	Temporary control Apr 2022	*Pending, Mar 2023 CND*	Sent Jul 2022

Shaded – next steps being evaluated; CND = U.N. Commission on Narcotic Drugs

Potency Summary – “Nitazenes”

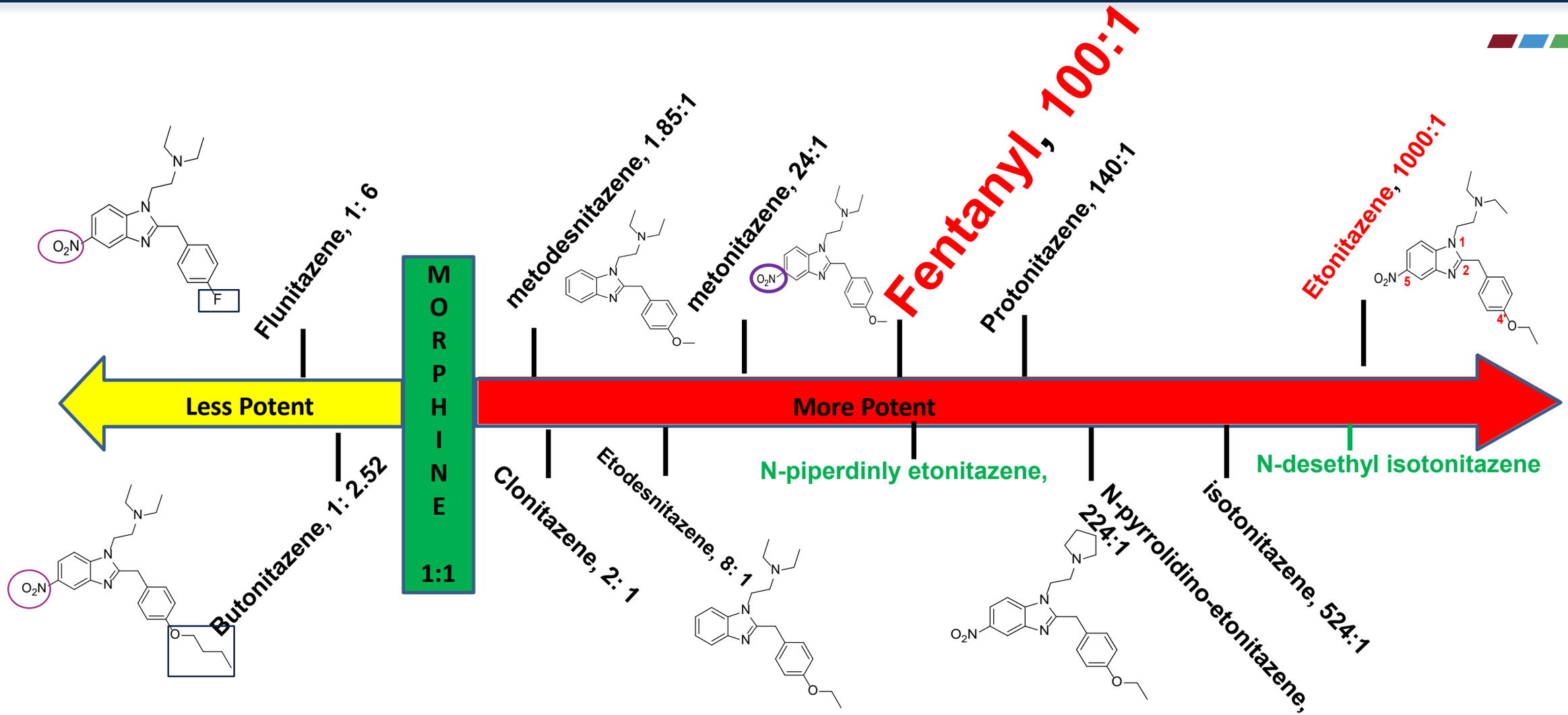


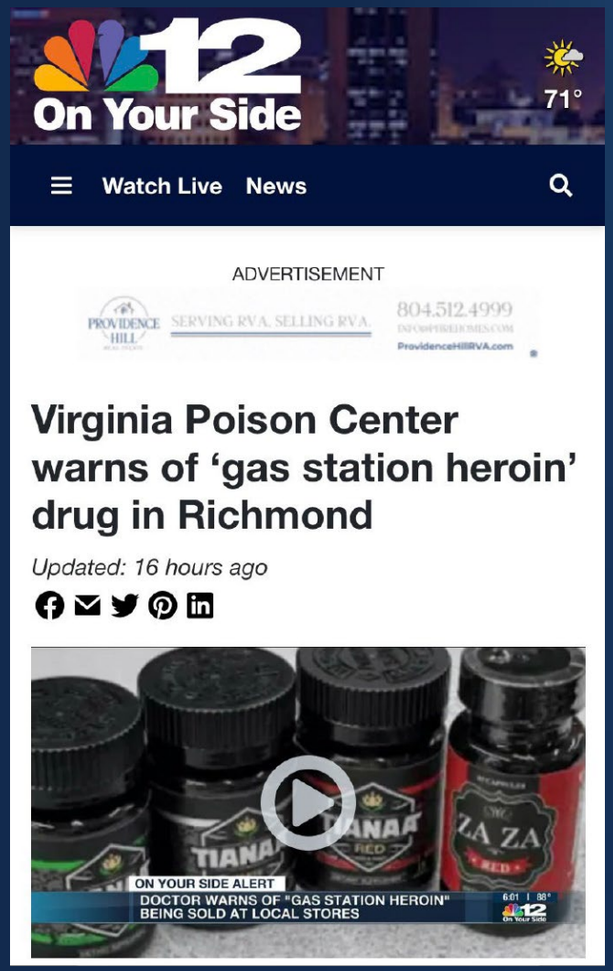
Diagram is not to scale. All data from preclinical analgesia study using rodents. ED_{50} (mice) ratio comparison to morphine . Reference: DEA Research Contracts (Gatch 2021; Paronis, 2021); Vandeputte et al., 2022

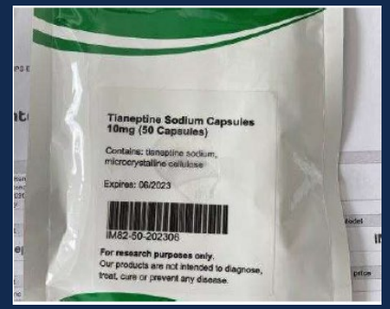
Designer Opioids + Xylazine

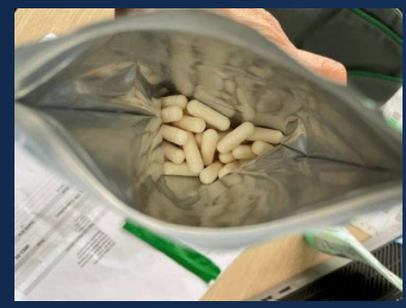
- Presence adds further complexity to already complicated issue
- Highly unpredictable substances alone
- Unknown if traditional responses work or work effectively – ex narcan, overdose could be final
- Timeline to Control Additional Designer Opioids
  - 2 additional “nitazenes” – pending
  - Other predicted “nitazenes” in testing to shorten a possible response
  - AP-238 and 2-Methyl-AP-237 – pending
- Xylazine under review with HHS and pending a recommendation

Tianeptine

- Antidepressant that stimulates the *mu*-opioid receptors at high doses
- Users describe effects and withdrawals similar to opioids
- Encountered in designer drug products
  - FDA clear these are not dietary supplements as being purported
- Drug is under FDA review

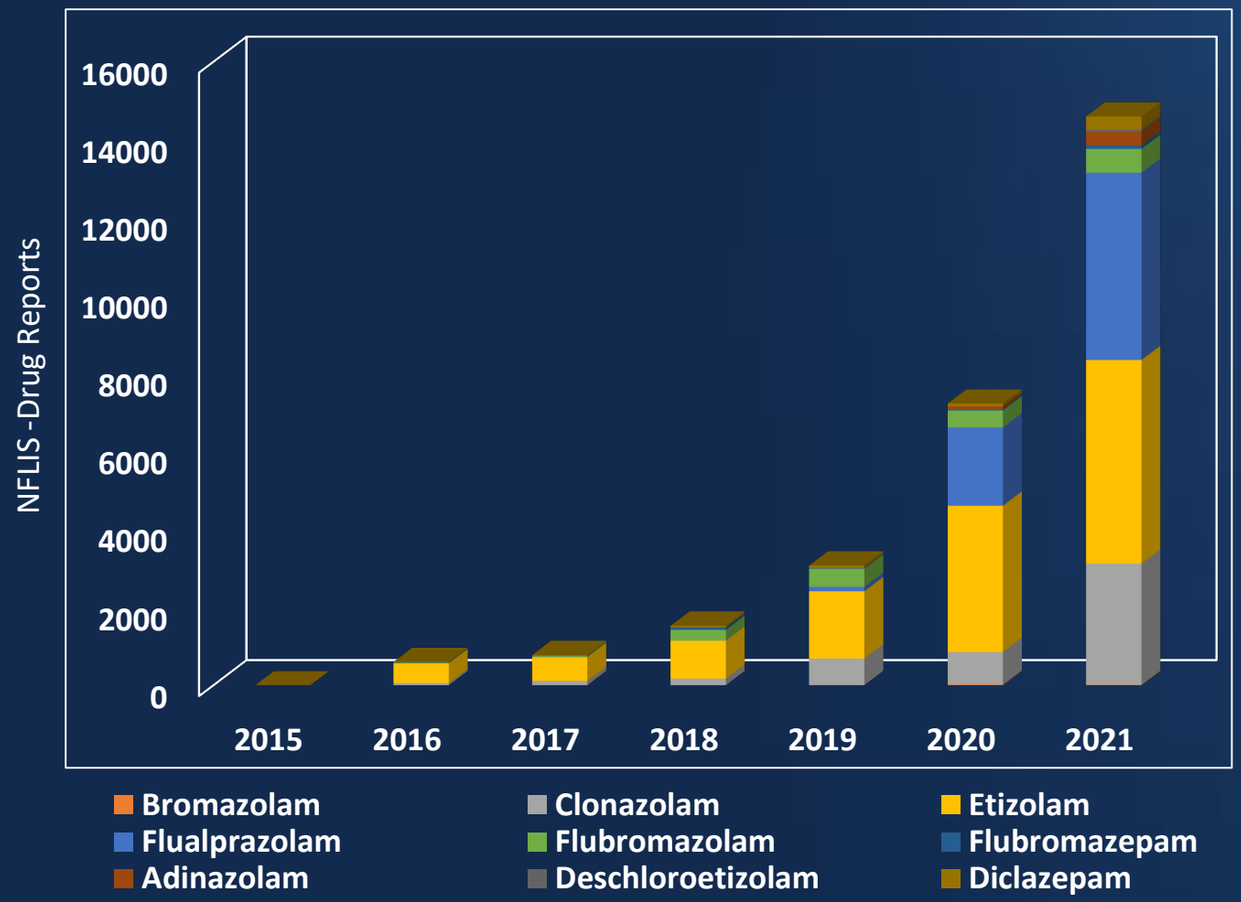






Designer Benzos

- Published a notice of intent to emergency control five benzodiazepines
- Waiting to finalize the action
- Once finalized, other designer benzos can be treated under the analogue provision
- Questions:
  - What happens at the end of the 2 years?
  - Does HHS recommend CI placement?



Butalbital Products Exemption

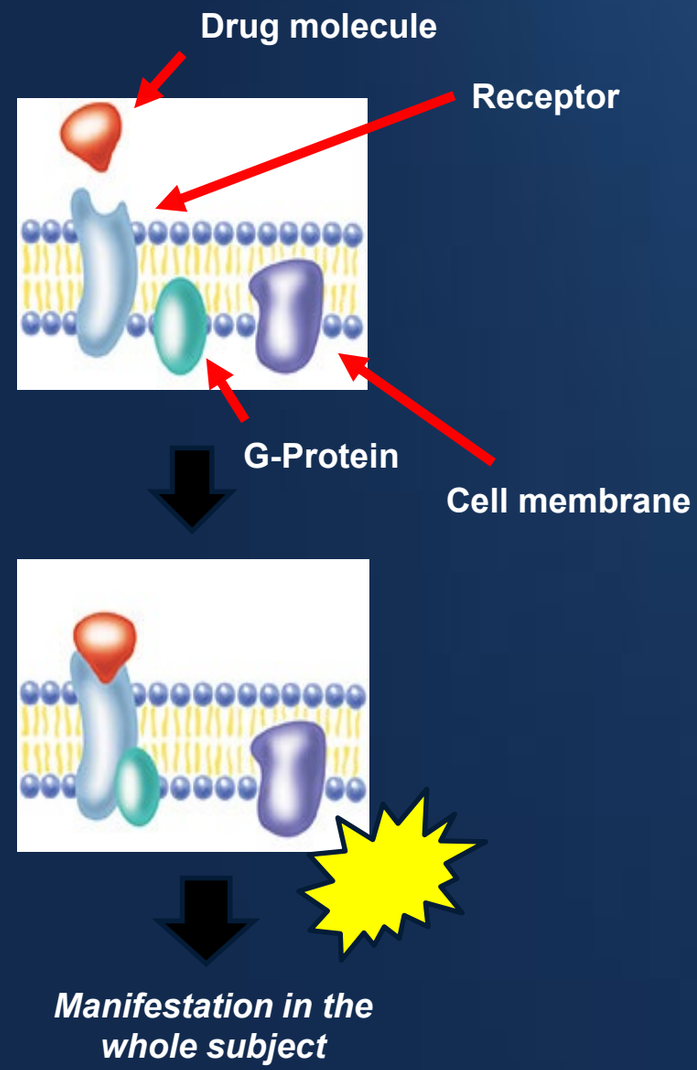
- Exemption dates back to 1967 and recommendation by a FDA panel
  - Fiorinal - CIII – butalbital (50 mg) + aspirin (325 mg) + caffeine (40 mg)
  - Fioricet - exempt – butalbital (50 mg) + acetaminophen (300 mg) + caffeine (40mg)
- Exemption used to draw users to gray market vendors
- Published notice of proposed rulemaking to remove the exemption on April 12, 2022 (started Dec 2012)
  - Collected comments (4)
  - No exemptions have been granted since May 2021
- Some manufacturers have already begun CIII labeling of previously exempt products

DEA Pharmacology Testing Program

Overview

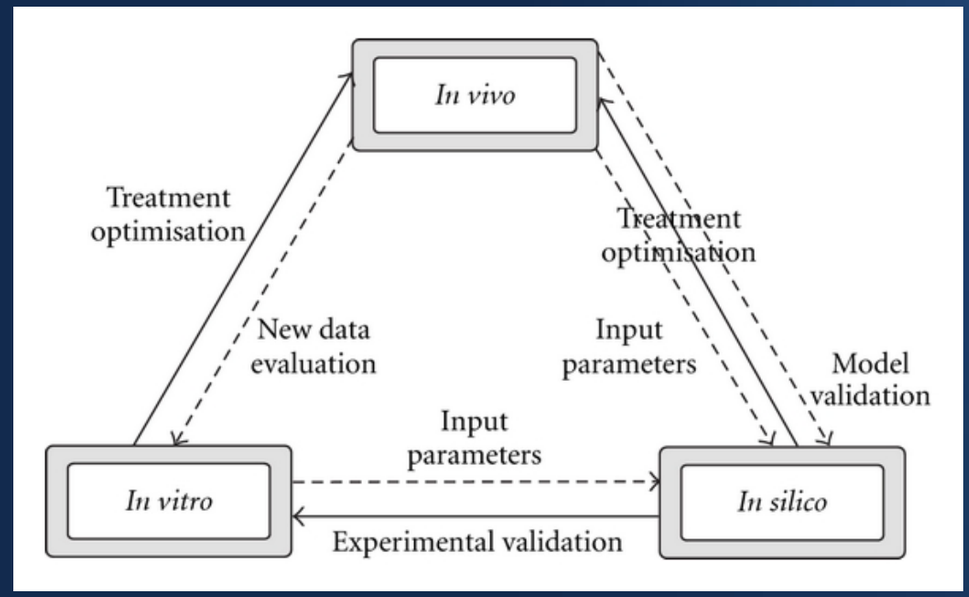
- **DEA contracts test new drug substances**

- **Informs:**
  - **Emergency control**
  - **HHS' evaluation to permanently control**
  - **International control**
  - **Federal analogue prosecutions**
  - **Sentencing considerations**
  - **Drug control policy and strategy development**



Evaluating a Drug for Abuse Potential

- **Predictive Data (*in silico*)**
  - Computational modeling
- ***in vitro* Data – Cellular Level**
  - Binding assays
  - Functional assays
- ***in vivo* Data – Animals**
  - Drug discrimination
  - Locomotor activity
  - Analgesia
- ***in vivo* Data – Humans**
  - Clinical studies/case reports



DEA TOX

- Began in May 2019 as a surveillance program aimed at detecting new psychoactive substances within the U.S.
- Goal - to gather intelligence on current and emerging psychoactive substances and communicate back to public health and law enforcement specific drugs in the AOR

https://www.deadiversion.usdoj.gov/dea_tox/index.html

DEA Toxicology Contract

DEA TOX
DRUG ENFORCEMENT ADMINISTRATION
TOXICOLOGY TESTING PROGRAM

Year	Submissions	Containing NPS	Containing Fentanyl	Containing Xylazine
2019	2	0	0	0
2020	126	61 (48.4%)	14 (11.1%)	0
2021	478	188 (39.3%)	201 (42.1%)	47 (9.8%)
2022	377	130 (34.5%)	191 (50.6%)	22 (5.8%)
2023*	29	16 (55.2%)	20 (69%)	5 (17.3%)
* As of 02/23/2023; 104 cases submitted in the past 10 days				

- 800 samples yearly capacity
- > 1200 reference drugs
- Results returned to submitting agency within 3 weeks

Cases pending (recently submitted):

Kentucky Poison Center – 49 samples
Illinois Poison Center – 3 samples
DEA Omaha FD – 2 samples
Knox County, TN Medical Examiner – 9 samples
King County Medical Examiner (Seattle, WA) – 25 samples
Utah Poison Center – 1 sample
Sedgwick County, KS Medical Examiner – 1 sample
Oregon Poison Center – 11 samples
Baltimore, MD Medical Examiner – 2 samples
DEA Austin, TX DO – 1 sample

Schedule I Researcher Activities & Checklist

- New Registrant
- New protocol (existing drug codes)
- New protocol (new drug codes)
- Amend protocol (increase drug quantity)
- Renewal
- Changes (name, address, etc.)

Investigator:

- ☐ Name, address, DEA registration number (if any)
- ☐ Institutional or company affiliation
- ☐ Qualifications, including **CV** with a list of publications

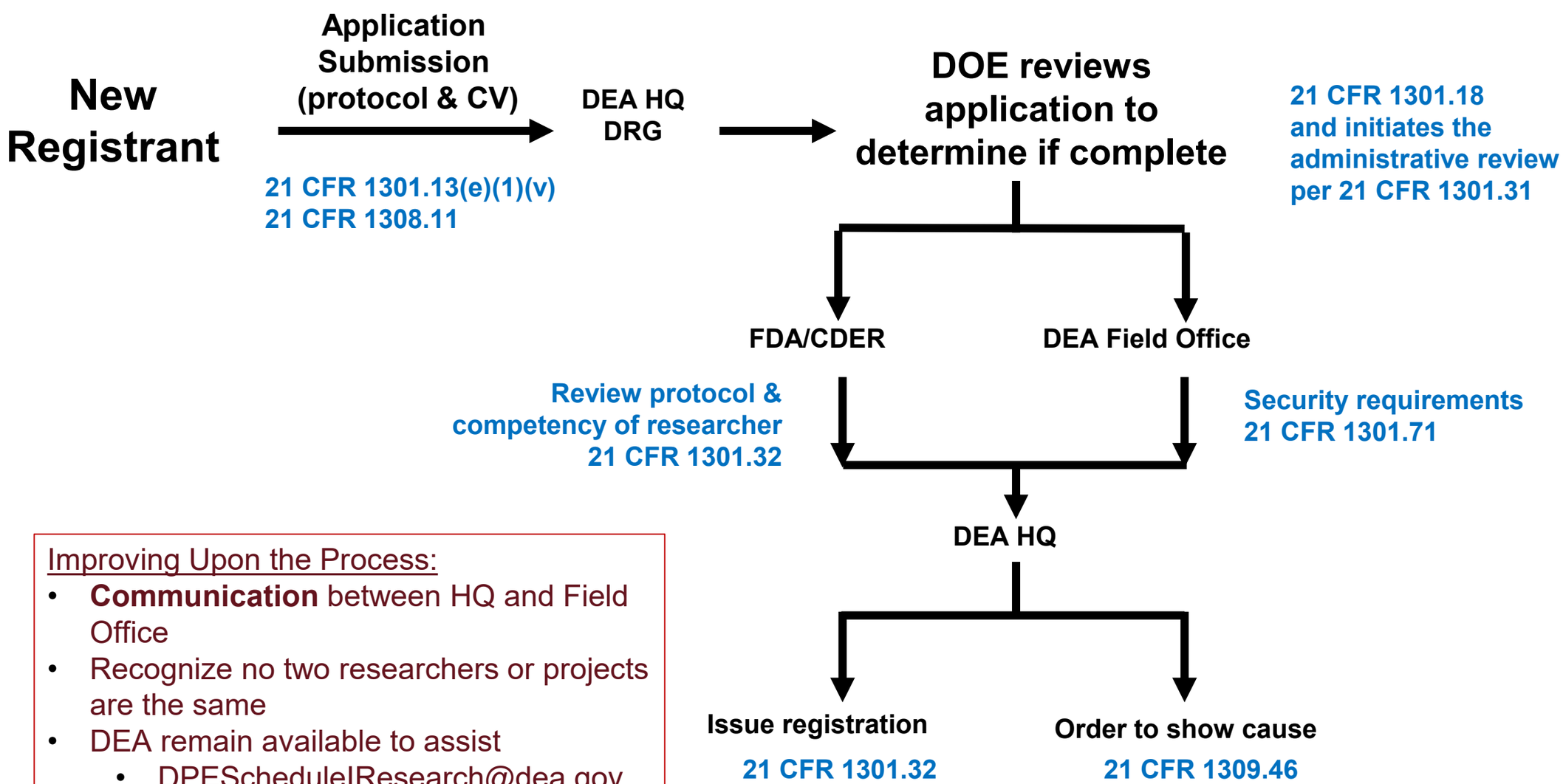
Research Project:

- ☐ Title of project
- ☐ Statement of the purpose
- ☐ Name of controlled substances (CS) involved, amount (**with justification**) of each needed and **source**.
- ☐ Research protocol (**detailed description of procedures**), including number and species of research subjects, dosage to be administered, route and method of administration, and **duration of project**.
- ☐ Location where research will be conducted.
- ☐ **Statement of security provisions** for storing and dispensing the CS(s) in order to prevent diversion.
- ☐ If investigator plans to manufacture or import the CS(s), statement of quantity to be manufactured or imported and sources of chemicals to be used or substance to be imported.

Authority (if applicable):

- ☐ Institutional approval
- ☐ Approval of a Human Research Committee for human studies.
- ☐ Indication of an approved active Notice of Claimed Investigational Exemption for a New Drug (IND) (number).
- ☐ Indication of an approved funded grant (number), if any.

Schedule I Researcher Approval Process



Improving Upon the Process:

- **Communication** between HQ and Field Office
- Recognize no two researchers or projects are the same
- DEA remain available to assist
  - DPEScheduleIResearch@dea.gov
  - https://www.deadiversion.usdoj.gov/

Conclusion

Let us know how we can assist

General mailboxes:

- DPE@dea.gov
- DPEScheduleIResearch@dea.gov