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, ∆8-THC, THCA, THCV, CBN, CBG, CBC, ∆10-THC, ∆8 and ∆9-THCO, synthetic vs. natural, etc.
- Recent letter to law firm reaffirming tetrahydrocannabinols synthesized from non-cannabis materials are not treated as “hemp”
Modification of the CSA
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**
  - Synthetic Drug Abuse and Prevention Act of 2012
- **Administrative**
  - Anabolic steroids
  - Cannabimimetic agents
- **Compliance with international treaties**
DEA Modifications to Drug Schedules

Petition

Drug Approval under FD&CA

DEA initiated review

Scheduling

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
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
• 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

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**Diagram Description**

1. **New Drug Application** → **FDA Submission** → **DHHS Initiates**
2. **Petition/DEA Initiation** → **DEA Review** → **if accepted** → **HHS Scientific & Medical Review** → **Accepted** or **Rejected**
3. **Substance placed under control** → **YES** → **FDA**
4. **Formal Rulemaking** → **Comments / Hearing?** → **Advisory Committee**
5. **Legislative** → **DEA Review Control?**
6. **Scheduling recommendation** → **HHS**

* = Industry interaction
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.

Number of Reports to NFLIS

- Cannabis/THC: 604,4
- Cocaine: 581,608
- Methamphetamine: 181,933
- Heroin: 88,851
- Hydrocodone: 38,012
- Alprazolam: 34,723
- Oxycodone: 29,563
- MDMA: 25,883
- Noncontrolled, non-narcotic: 12,821
- Methadone: 9,202

Source: DEA, NFLIS Public Resource Library Static Tables.
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
If the presence of illicit fentanyl alone is not bad enough - other substances are being either mixed with fentanyl or abused with fentanyl.

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
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

![Image of a 30 mL bottle]

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

![Image of a gummy bear]

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)

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”

Challenge for forensic labs and regulators

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.
Source of delta-8 THC

Where did come from?

“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.”

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

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. 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 (65-70%), it also contains about 2-6% delta-9-THC. 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
Another patchwork of laws at the state and local level

States that have banned *delta*-8 THC

<table>
<thead>
<tr>
<th>State</th>
<th>State</th>
</tr>
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<tbody>
<tr>
<td>Alaska</td>
<td>Nevada</td>
</tr>
<tr>
<td>Colorado</td>
<td>North Dakota</td>
</tr>
<tr>
<td>Delaware</td>
<td>Oregon</td>
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<tr>
<td>Idaho</td>
<td>Rhode Island</td>
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<tr>
<td>Iowa</td>
<td>Utah</td>
</tr>
<tr>
<td>Montana</td>
<td>Vermont</td>
</tr>
<tr>
<td>New York</td>
<td>Washington</td>
</tr>
</tbody>
</table>

States that regulate *delta*-8 THC sales

<table>
<thead>
<tr>
<th>State</th>
<th>State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connecticut</td>
<td>Michigan</td>
</tr>
</tbody>
</table>

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

December 2018, Agricultural Improvement Act Signed into Law
Fentanyl-Related Substances

- China played a significant role as a 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

Monthly NFLIS Reports of Non-Controlled Fentanyl-Related Substances (FRS), 2015-2018
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
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

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
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, dipyrrone, 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-piperidine ethylene ketal
What is captured under List I .....
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.
Prioritize the most **prevalent, persistent, and harmful** 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
Potency Summary – “Nitazenes”

More Potent

Fentanyl, 100:1

Morphine, 140:1

Protonitazene, 524:1

N-desethyl isotonitazene

N-piperdinly etonitazene,

Metonitazene, 24:1

Metodesnitazene, 185:1

Etodesitazene, 8:1

Clonitazene, 2:1

Butonitazene, 1:1

2:5:2

Less Potent

Flunitazene, 1:6

Diagram is not to scale. All data from preclinical analgesia study using rodents. ED50 (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
  o 2 additional “nitazenes” – pending
  o Other predicted “nitazenes” in testing to shorten a possible response
  o 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

Manifestation in the whole subject
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
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.
### DEA Toxicology Contract

<table>
<thead>
<tr>
<th>Year</th>
<th>Submissions</th>
<th>Containing NPS</th>
<th>Containing Fentanyl</th>
<th>Containing Xylazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2020</td>
<td>126</td>
<td>61 (48.4%)</td>
<td>14 (11.1%)</td>
<td>0</td>
</tr>
<tr>
<td>2021</td>
<td>478</td>
<td>188 (39.3%)</td>
<td>201 (42.1%)</td>
<td>47 (9.8%)</td>
</tr>
<tr>
<td>2022</td>
<td>377</td>
<td>130 (34.5%)</td>
<td>191 (50.6%)</td>
<td>22 (5.8%)</td>
</tr>
<tr>
<td>2023*</td>
<td>29</td>
<td>16 (55.2%)</td>
<td>20 (69%)</td>
<td>5 (17.3%)</td>
</tr>
</tbody>
</table>

* 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

**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.
**New Registrant Application Submission (protocol & CV)**

- **DEA HQ**
- **DRG**

**DOE reviews application to determine if complete**

- **FDA/CDER**
- **DEA Field Office**

- **Security requirements**
  - 21 CFR 1301.18
  - and initiates the administrative review per 21 CFR 1301.31

**21 CFR 1301.13(e)(1)(v)**
**21 CFR 1308.11**

**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/

**Issue registration**
**Order to show cause**

- 21 CFR 1301.32
- 21 CFR 1309.46
Conclusion

Let us know how we can assist

General mailboxes:

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