Drug and Chemical Evaluation Section (ODE) Chemical Role includes:

- Determination of chemicals used in the manufacture of controlled substances.
- Use of existing regulatory mechanisms to control compounds used in this manufacture.
Current Activities

- Iodine Regulations (NPRM)
- Sodium Permanganate
- Elimination of Ephedrine/Pseudoephedrine Chemical Mixture Exemptions
- Control of Precursors to Fentanyl
- Positional Isomers Definition
Methamphetamine Production
Iodine Control

- Iodine used as reagent in Methamphetamine production
- Number one U.S. clandestinely produced drug
DEA and State and Local Law Enforcement Methamphetamine Seizures (Includes Labs, dump sites, glassware and equipment seizures) Calendar Years 1999 – 2005 (Reported through June 2006)
Methamphetamine Production

- P2P + Methylamine → d,l-methamphetamine
- Ephedrine + Hydriodic Acid + Red-P → d-methamphetamine
Methamphetamine Production

- Ephedrine + Hydriodic Acid + Red-P → d-methamphetamine
- Pseudoephedrine + Iodine + Red-P → d-methamphetamine
  - or Ephedrine Crystals
- Pseudoephedrine + Iodine + Red-P → d-methamphetamine
  - or Ephedrine Tincture*

* Hydrogen Peroxide used to precipitate out crystals
“Mexican Crime Group Methamphetamine ‘SUPER LAB’ Seizure in California.”
“Two Large Capacity Methamphetamine Clan Labs.”
Existing Iodine Controls

• List II Chemical
• Threshold 0.4 kilograms
• Only domestic transactions regulated
• Import/Export transactions exempted
• Iodine tinctures (considered chemical mixtures) are exempt
Iodine Problem

• Widely used in clandestine laboratories
• Since tinctures are exempt, lab operators have discovered they can acquire unregulated 7% tincture, add hydrogen peroxide and precipitate out iodine crystals for clan lab use
• Scope of diversion is an international problem
Proposed Changes to Iodine Regulations

- NPRM Published August 11, 2006 with 60-day comment period
- Move from List II to List I
  - Impose registration requirement
- Add Import/Export Controls
- Remove threshold so that all transactions regulated regardless of size
- Control chemical mixtures at concentration level which will regulate 7% iodine tincture
  - Used primarily in livestock/horse industry
  - No household use
Iodine Control

- Will not adversely impact any of the iodine products sold in retail drug store setting
- Will exempt iodine-povidone complexes (all concentrations)
- Will not regulate iodine 2% tincture
- Will not control any of the iodide compounds sold via prescription or radiolabeled for diagnostic purposes.
- Currently reviewing comments and considering further exemptions where appropriate
Sodium Permanganate
Sodium Permanganate

- Direct Substitute for Potassium Permanganate in cocaine processing
- NPRM to control as a List II chemical published March 1, 2005
- Final Rule published October 17, 2006
Cocaine Production

Cocaine is extracted from the coca leaf after the leaves are picked and dried.
TYPES OF CHEMICALS HISTORICALLY USED IN THE PRODUCTION OF COCAINE

SOLVENTS - Methyl Ethyl Ketone (MEK), Methyl isobutyl Ketone (MIBK), Acetone, Ethyl ether, Toluene, Kerosene

ACIDS - Sulfuric Acid
        Hydrochloric Acid

BASES - Calcium, Sodium or Potassium Carbonate, Calcium Oxide
         Ammonia Water

OXIDANTS - Potassium Permanganate
PRODUCTION OF ILLICIT COCAINE
FOUR STEPS

1. COLLECTION OF COCA LEAVES
2. PRODUCTION OF COCA PASTE BY SOLVENT PROCESS OR ACID PROCESS
3. PRODUCTION OF COCAINE BASE
4. PRODUCTION OF COCAINE HYDROCHLORIDE
Production of Coca Base

**Coca Paste**
- Add dilute sulfuric acid;
- Add potassium permanganate;
- Mix and filter

**Solution of Acid with Cocaine**
- Add ammonia water; mix; filter

**Cocaine Base**

Solids

Liquid
Sodium Permanganate

- Direct Substitute for Potassium Permanganate
- Potassium permanganate one of the most important chemicals for cocaine production
- U.S. producers changing production toward increase production of Sodium Permanganate
- Sodium Permanganate available as a 40% solution has advantage of being miscible with water in all proportions (Potassium Permanganate has only 6.38% solubility in water)
Proposed Controls for Sodium Permanganate

- Since directly substitutable for Potassium Permanganate
- Propose Same level of Control
- List II – No Registration
- Thresholds: 55 kgs domestic, 500 kgs import/export
- Chemical Mixtures <= 15 percent exempt
Ephedrine/ Pseudoephedrine Exemptions
Ephedrine/ Pseudoephedrine Exemptions

This Interim Rule announces the removal of the CSA exemptions for chemical mixtures containing ephedrine and/or pseudoephedrine.

• In a Final Rulemaking [68 FR 23195] published on May 1, 2003, DEA initially created an exemption from CSA chemical regulations for all chemical mixtures containing five percent or less total ephedrine/pseudoephedrine.

• Additionally, that rulemaking created an exemption for chemical mixtures consisting of unaltered harvested plant material containing ephedrine alkaloids (e.g. ephedra).

• This Interim Rule, however, removes these two exemptions. Therefore, these materials shall now be subject to all CSA provisions.
• The Combat Methamphetamine Epidemic Act of 2005 (CMEA) added additional controls on ephedrine and pseudoephedrine and mandated that DEA limit the domestic production and importation of materials containing ephedrine and pseudoephedrine to quantities necessary for medical, scientific and other legitimate purposes.

• DEA has growing concerns regarding ephedra and dietary supplements containing ephedra, and their use as the source of the precursor material for use in the illicit production of methamphetamine.

• While the FDA has taken action to eliminate ephedra dietary supplements from the U.S. market, DEA has seen increases in number of import requests for ephedra, leading to a concern that these products are being diverted for use in illicit manufacture of methamphetamine.
• Given these concerns, and Congressional direction to limit the importation of materials containing ephedrine/pseudoephedrine, DEA is eliminating the exemptions for this material.
Clandestine Fentanyl
Pharmacology

- Synthetic opioid
- Schedule II narcotic
- Low therapeutic index
  - Euphoria vs respiratory depression

- Effects are similar to morphine and heroin, but with two principle differences:
  1) Duration of action (rapid onset, shorter acting)
  2) Potency (much greater potency)
     - 50 - 100x more potent analgesic than Morphine
     - 30 - 50x more potent analgesic than Heroin
     - Potency depends on route of administration and the effect being measured
History of Fentanyl Abuse

- 1970’s to present – Abuse of injectables
  - Medical professionals (doctors/nurses/pharmacists) often in a hospital setting

- 1990’s to present – Abuse of transdermal patch & Troche

- 2000’s – Clan labs making fentanyl
  - 6 Fentanyl clan labs since 2000
  - 5 of which are known or suspect to have used Siegfried Method
  - DEA preparing regulations to control precursor chemicals
  - 499 Confirmed Death + 288 Suspected deaths in U.S.
Illicitly Manufactured Fentanyl-Related Deaths by Location Since 3/4/2005
(DEA Compiled: 10/12/06)

<table>
<thead>
<tr>
<th>Location</th>
<th>Confirmed Deaths</th>
<th>Suspected Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chicago, Illinois</td>
<td>214</td>
<td>2</td>
</tr>
<tr>
<td>Detroit, Michigan</td>
<td>150</td>
<td>62</td>
</tr>
<tr>
<td>Philadelphia, PA/Camden, NJ/Wilmington, DE</td>
<td>215</td>
<td>14</td>
</tr>
<tr>
<td>Rest of PA</td>
<td></td>
<td>57</td>
</tr>
<tr>
<td>New York State</td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>St. Louis, Missouri</td>
<td>27</td>
<td>14</td>
</tr>
<tr>
<td>Other areas</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Total Deaths =&gt;</td>
<td>606</td>
<td>207</td>
</tr>
</tbody>
</table>
Illicitly Manufactured Fentanyl-Related Deaths/Week in U.S. From March 4, 2005 – August 5, 2006
(Total DEA Confirmed Deaths Graphed: 606)

Week (Sun. to Sat.) Compiled 10/12/2006
Number of Deaths
Clandestine Lab in Toluca, Mexico

Sunday, May 21, 2006 PGR/SIEDO and AFI
Siegfried Method
Control of Precursors

• DEA is moving to control precursors:
  – NPP (N-phenethyl-4-piperidone) as a listed chemical in List I
  – ANPP (4-anilino-N-phenethyl-4-piperidine) as an immediate precursor in Schedule II
Legitimate Uses Of NPP

- Legitimate uses of NPP:
  - Pharmaceutical Industry
  - Pharmaceutical R&D to synthesis experimental compounds
  - Analytical Reference Standards

- Drugs prepared from NPP:
  - Fentanyl
  - Carfentanyl
  - Cinitapride – gastrointestinal motility agent
  - Fenspiride – nonsteroidal anti-inflammatory agent

- Specialty Chemical
  - Low volume
  - Only 6 domestic chemical suppliers of NPP
  - Only 24 domestic purchases since January 1, 2004
Fentanyl Synthesis: Siegfried Method

NPP → ANPP → Fentanyl
Siegfried Method: Making ANPP

1. Add Aniline/Molecular Sieves
2. Stir 24 hrs at room temp
3. Add NaBH4
4. Stir for 3 hrs at room temp
5. Clean up stage: Add H2O & HCl
6. Extraction
7. Dry
8. Isolate ANPP crystals
9. Aqueous Phase
10. NaOH
Siegfried Method: Making Fentanyl

- ANPP
- Add propionyl chloride slowly
- Stir 1 hr at room temp
- Extract & Dry
- Fentanyl
November 2005, law enforcement seized a lab in the LA area suspected to be Fentanyl lab.

Chemists analyzed the samples submitted and confirmed fentanyl and MDA present.

A 5 kilogram bag of “NPP” (1-phenethyl-4 piperidone) precursor was seized.
Definition of Positional Isomers

- This Rulemaking establishes a specific, technical definition for the term “positional isomer” as it relates to Schedule I hallucinogens.
Background: Positional Isomers

• The CSA (21 U.S.C. 802(14) and 21 U.S.C. 812(c)(I)(c)) specify which hallucinogenic compounds are considered Schedule I Controlled Substances. The CSA states that all salts, isomers and salts of isomers of these compounds are also Schedule I Controlled Substances.

• Under 21 CFR 1308.11(d), the CSA states that the term isomers shall include “optical, positional and geometric isomers”.

• Optical and geometric isomerism easily determined.

• The definition will include precise language that will allow for an unambiguous determination of which isomers of Schedule I hallucinogenic substances are considered to be “positional”, and therefore subject to Schedule I control.
• The addition of a definition for the term “positional isomer” will assist legitimate research and industry in determining the control status of materials that are isomers of Schedule I hallucinogens.

• While DEA will remain the authority on ultimately determining the control status of a given material, providing a specific definition for “positional isomer” will ensure consistent criteria are utilized in making these determinations.

• The addition of a definition for the term “positional isomer” will not result in the control of additional substances or have a negative impact on legitimate researchers or industry working with isomers of Schedule I hallucinogenic substances.
Status: Positional Isomers

• A Notice of Proposed Rulemaking (NPRM) was Published in Federal Register on May 25, 2006

• A final rule is being circulated for signature.
Christine A. Sannerud, Chief

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