



U.S. Department of Justice  
Drug Enforcement Administration

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Washington, D.C. 20537

APR 17 1998

Docket Management Branch  
(HFA-305)  
Food and Drug Administration  
12420 Parklawn Drive  
Room 1-23  
Rockville, Maryland 20857

Dear Sir:

This is in reference to Docket No. 98N-0148 regarding the international drug scheduling of dihydroetorphine, remifentanil and ephedrine. The Drug Enforcement Administration (DEA) has reviewed the available data regarding the abuse and trafficking of dihydroetorphine, remifentanil and ephedrine. These data could be incorporated into the critical reviews to be used for the 31st World Health Organization (WHO) Expert Committee on Drug Dependence.

Enclosed are DEA's summaries regarding the abuse of dihydroetorphine, remifentanil and ephedrine. The data compiled regarding ephedrine show its extensive use in the clandestine manufacture of methamphetamine and other controlled substances. The review of remifentanil and dihydroetorphine show that they meet the requirement for Schedule II controls in the United States. Comments on the United Nations notification regarding the Spanish proposal (NAR/CL.2/1998) will be submitted under separate cover.

We are pleased to be providing such important data to the Food and Drug Administration for inclusion in the U.S. submission to WHO for its critical review and prereview documents.

Sincerely,

Frank L. Sapienza, Chief  
Drug & Chemical Evaluation Section

Enclosures

98N-0148

C5-

DEA Data for the  
Critical Review Document for Remifentanyl

INN: Remifentanyl

Substance

**Known Source:** Glaxo Wellcome is the sole manufacturer and supplier. Bulk remifentanyl is imported into the United States for formulation into dosage units.

**Chemical Name:** 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid methyl ester, hydrochloride salt]

**Group/Chemical Relatives:** Fentanyl methyl ester.

**Metabolism, Pharmacokinetics:**

Pharmacology

Remifentanyl is a selective mu-opioid agonist. As a fentanyl analogue, its potential for abuse and physical dependence is similar to that of alfentanil and sufentanyl.

Therapeutic Aspects

**Indications:**

In the United States, remifentanyl is marketed under the trade name ULTIVA as an intravenous agent for induction and maintenance of anesthesia and monitored analgesic. The following products are available:

- (1) 1 mg remifentanyl base lyophilized powder in 3 mg vials
- (2) 2 mg remifentanyl base lyophilized powder in 5 mg vials
- (3) 5 mg remifentanyl base lyophilized powder in 10 mg vials

**Geographic Availability:** Remifentanyl was approved for marketing in the United States on July 12, 1996.

Adverse Effects

**Physical:**

**Psychiatric:**

Dependence Potential

**Preclinical:**

**Clinical:**

Actual Abuse

On November 5, 1996, remifentanyl, and salts thereof, was placed into Schedule II of the United States Controlled Substances Act.

**Abuse Pattern:** No epidemiologic information is available.

**Illicit Traffic:** DEA is not aware of any evidence of illicit trafficking of remifentanyl.

Preliminary Evaluation (by reviewer)

DEA Data for the  
Critical Review Document for Dihydroetorphine

INN: Dihydroetorphine

Substance

**Known Source:** No source in United States

**Chemical Name:**

**Group/Chemical Relatives:** Dihydroetorphine belongs to etorphine group. It is a thebaine derivative.

**Metabolism, Pharmacokinetics:**

Pharmacology

Therapeutic Aspects

**Indications:** Dihydroetorphine is not marketed or used medically in the United States

**Geographic Availability:** It is not available in the United States.

Adverse Effects

**Physical:**

**Psychiatric:**

Dependence Potential

**Preclinical:**

**Clinical:**

Actual Abuse

As a thebaine derivative, dihydroetorphine is controlled in Schedule II of the federal Controlled Substances Act in the United States.

**Abuse Pattern:** No epidemiologic information is available.

**Illicit Traffic:** DEA is not aware of any evidence of illicit trafficking of dihydroetorphine.

Preliminary Evaluation (by reviewer)

**EPHEDRINE:  
Evidence of Abuse**

**Drug and Chemical Evaluation Section  
Office of Diversion Control  
Drug Enforcement Administration  
April 10, 1998**

In the United States, ephedrine is available over-the-counter (OTC) for use as a bronchodilator, decongestant, and in allergy products. In recent years, dietary supplements have been marketed in the United States which contain various quantities of ephedra alkaloids. Some of these products are posing a health risk to the user. The Centers for Disease Control has issued a report of adverse events associated with ephedrine-containing products (previously provided).

Ephedrine has long been associated with drug abuse and illicit activity involved in the clandestine manufacture of controlled substances. In the late 1970's and 1980's, ephedrine was found in many stimulant "look-alike" products, which resulted in serious health problems. In recent years, FDA has received reports of young people abusing OTC ephedrine drug products for "kicks" and as an "upper" or "energizer". Many of these cases resulted in adverse reactions or overdoses treated in emergency room visits.

DEA has found that ephedrine is used as precursor material for the clandestine manufacture of controlled substances. Ephedrine is one of the primary precursors used in the illicit manufacture of methamphetamine and methcathinone. As such, it contributes to the public health risk associated with these substances. In recent years, at least 26 U.S. states have placed additional controls on ephedrine, and additional states have proposed legislation. The DEA data regarding ephedrine primarily represents its diversion for use in illicit laboratories.

**Federal Laws Regulating Ephedrine**

Although it is not a controlled substance under the federal Controlled Substances Act (CSA) in the United States, ephedrine and its products are regulated as a listed chemical under that law.

There are three Acts that have amended the CSA to provide a mechanism for preventing the diversion of legitimately produced chemicals into the illicit market.

The Chemical Diversion and Trafficking Act of 1988 (CDTA) placed under Federal control the distribution of twelve precursor and eight essential chemicals as well as the distribution of tableting and encapsulating machines. Ephedrine, its salts, optical isomers and salts of optical isomers were controlled under this Act. Exemptions for all lawfully marketed ephedrine pharmaceutical products were included. The Act requires manufacturers, distributors, importers and exporters of threshold amounts of these chemicals to:

- obtain proof of identity for customers,
- maintain retrievable receipt and distribution records and
- report to the Drug Enforcement Administration (DEA) any suspicious orders of a listed chemical or any order placed by an individual under investigation by DEA.
- DEA has the authority to stop import or export shipments not destined for legitimate medical, scientific, or commercial use. For transactions with new customers, importers and exporters must, in addition to the above, file an import/export declaration with DEA at least 15 days prior to the date of import or export.

The CDTA had a significant impact on the diversion of bulk ephedrine for use in the illicit production of controlled substances. Traffickers, however, quickly exploited a loophole in the CDTA and turned to exempt OTC ephedrine products as a source of ephedrine for clandestine laboratories.

The Domestic Chemical Diversion Control Act of 1993 (DCDCA) builds on the CDTA, extends the government's authority, and addresses loopholes that were exploited by traffickers. Controls on ephedrine, a List I chemical, were extended to certain ephedrine pharmaceutical products. The DCDCA

- requires manufacturers, distributors, importers and exporters of List I chemicals to register with DEA;
- requires manufacturers, distributors, importers and exporters of List I chemicals to maintain adequate security over List I chemicals;
- requires U.S. based brokers or traders involved in shipments across an international border, other than a U.S. border, to file a declaration at least 15 days prior to the date of the transaction;
- requires reporting of annual production data by manufacturers of List I and List II chemicals;
- removes the general exemption for chemical mixtures. Specific mixtures may be exempted by DEA, and
- removes the exemption for single-entity ephedrine products.

The DCDCA had a significant impact on the use of single entity ephedrine products in clandestine laboratories. Traffickers then switched to ephedrine/guaifenesin products and pseudoephedrine products as a source of precursor material.

The Comprehensive Methamphetamine Control Act of 1996 (MCA) broadened controls on listed chemicals used in the production of methamphetamine, increased penalties for the trafficking and manufacture of methamphetamine and listed chemicals, and expanded regulatory control to include the distribution of lawfully marketed drug products which contain the listed chemicals ephedrine, pseudoephedrine, and phenylpropanolamine. Under the MCA:

- Sales of OTC ephedrine combination products, pseudoephedrine products, and phenylpropanolamine products above threshold levels are subject to the record keeping, reporting, registration and import/export notification provisions of the CSA. DEA, however, has proposed to exempt retail distributors, in specified circumstances, from the registration requirement. The threshold remains zero for ephedrine products which do not contain another active ingredient.

#### **STRIDE Data**

The System to Retrieve Information from Drug Evidence (STRIDE) provides data on drug evidence analyzed by DEA laboratories. STRIDE was examined for ephedrine for the period January 1, 1992 through December 31, 1997. There are over 2,166 separate laboratory exhibits for ephedrine indicating a substantial amount of law enforcement activity surrounding this drug.

During this 6 year period, there are over 2166 separate laboratory exhibits for ephedrine, involving 9 million tablets, 5,500 capsules, 22,000 kilograms of powdered material, and 73,000 mls of liquid. These exhibits were submitted for analysis in 857 separate DEA and non-DEA cases in 43 states and the District of Columbia.

Approximately 49% of the exhibits in STRIDE were specifically documented as being material obtained during seizures of clandestine laboratories, accounting for 855,000 tablets and capsules, and 956,000 gms of ephedrine in powdered and liquid form.

The remainder of the exhibits in STRIDE represent over 1,100 exhibits, 553 and non-DEA cases, and over 8 million ephedrine

tablets, 4,300 capsules, over 21,000 kilograms of powdered or liquid material. It is likely that much of this material was destined for illicit laboratories. Approximately 7% of these cases involved the seizure of millions or hundreds of thousands of tablets or grams of ephedrine each. Approximately 80% of these large seizures took place in California, 5% in Texas and 4% in Colorado.

DEA has begun to review the specific case files where large amounts of ephedrine was seized or purchased. In the ten cases that represented the largest quantities of ephedrine (over 500,000 tablets or grams), it was evident that the ephedrine was destined for clandestine labs. These ten cases accounted for over 5 million ephedrine tablets and 19,000 kilograms of powdered material. These seizures were made in many different US states, including California, Texas, Arizona, Michigan, Nevada, Washington and New Mexico. The above mentioned laboratory seizures and cases have been excluded from consideration of the actual abuse of ephedrine.

The remaining 543 DEA and non-DEA cases involve 3 million ephedrine tablets, 4,000 capsules and 3 kilograms of powdered or liquid material. Approximately 35% of these cases involve the seizure of thousands and tens of thousands of ephedrine tablets, capsules or powdered material. It is likely that many of these cases involving larger quantities are related to clandestine laboratory activities. In addition, there are over 700 exhibits (approximately 300 cases) that involve quantities of less than 200 tablets each. These cases involve a total of 23,000 capsules and tablets and 326 grams of ephedrine. These cases may be associated with abuse of ephedrine, but DEA has not had the opportunity to review these remaining 300 cases.

### **Clandestine Laboratory Seizures**

The number of clandestine laboratories manufacturing methamphetamine have increased dramatically since 1993. During calendar year 1997, there were a total of 1375 laboratory seizures, of which 1352 (98%) were methamphetamine laboratories. Of these 1352 methamphetamine laboratories, 10% involved the use of ephedrine combination tablets, and 85% involved the use of pseudoephedrine tablets.

### **Conclusion**

Large quantities of ephedrine, both in bulk and pharmaceutical dosage forms, have been trafficked and used in the clandestine synthesis of controlled substances.

U.S. DEPARTMENT OF JUSTICE  
FEDERAL BUREAU OF INVESTIGATION

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12420 Parklawn Dr, Rm 1-23  
Rockville MD 20857