WHO QUESTIONNAIRE
FOR REVIEW OF DEPENDENCE-PRODUCING PSYCHOACTIVE SUBSTANCES
BY THE
THIRTY-FOURTH EXPERT COMMITTEE ON DRUG DEPENDENCE

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1. LEGITIMATE USE OF THIS SUBSTANCE

1.1 Is the substance currently registered as a medical product? Yes (See approved package insert for Stadol nasal spray, Attachment 1)

If "Yes", since when (Year of marketing)?

Butorphanol tartrate was approved for marketing in 1978 by the Food and Drug Administration (FDA) within the U.S. Department of Health and Human Services (HHS). Butorphanol and its salts are currently controlled in Schedule IV under the U.S. Controlled Substances Act (CSA).

Both injection and nasal spray formulations of butorphanol tartrate are indicated for the management of pain when the use of an opioid analgesic is appropriate. The injection formulation is also indicated as a preoperative or preanesthetic medication, as a supplement to balance anesthesia, and for the relief of pain during labor.

Butorphanol tartrate is available as injections of 1 mg/mL and 2 mg/mL strengths, and as nasal spray of 1 mg/spray strength. The injection formulation is marketed under the trade name of Stadol and under generic names of butorphanol tartrate or butorphanol tartrate preservative-free. The nasal spray formulation is marketed under the name of butorphanol tartrate. Currently, four pharmaceutical companies are producing generic drug forms of injectable formulations containing butorphanol tartrate and three pharmaceutical companies are producing generic drug forms of the nasal spray formulation. Approximately 600,000 prescriptions were dispensed for butorphanol products in 2004.

Butorphanol Products Approved For Use in Humans

Trade name	*Dosage form*	*Strength(s)*	*Indication(s)*
Stadol	Injectable	2 mg/ml	For the relief of moderate to severe pain
Stadol Preservative free	Injectable	1, 2 mg/ml	For the relief of moderate to severe pain
Butorphanol Tartrate	Injectable	1, 2 mg/ml	For the relief of moderate to severe pain
Butorphanol Tartrate Preservative free	Injectable	1, 2 mg/ml	For the relief of moderate to severe pain
Butorphanol Tartrate	Nasal Spray, Metered	1 mg/spray	For the relief of moderate to severe pain

Currently, there are two pharmaceutical company is producing a generic drug form of butorphanol tartrate injection for use in animals.

Butorphanol Products Approved For Use in Animals

Trade name	*Dosage form*	*Strength(s)*	*Indication(s)*
Torbutrol	Tablet	1, 5, 10 mg	For the relief of chronic nonproductive cough associated with tracheobranchitis, tracheitis tonsillitis, laryngitis, and pharyngitis associated with inflammatory conditions of the upper respiratory tract in dogs
Torbutrol Injection	Injectable	0.5 mg/ml	Same as Torbutrol
Torbugesic-SA	Injectable	2 mg/ml	For the relief of pain in cats caused by major or minor trauma or pain associated with surgical procedures
Torbugesic	Injectable	10 mg/ml	For the relief of pain associated with colic and postpartum pain in horses and yearlings
Dolorex	Injectable	10 mg/ml	Same as Torbugesic
Butorphanol Tartrate Injection	Injectable	10 mg/ml	Same as Torbugesic
Vetus Torphaject	Injectable	10 mg/ml	Same as Torbugesic
Butorject Injection	Injectable	10 mg/ml	Same as Torbugesic
Equanol Injection	Injectable	10 mg/ml	Same as Torbugesic
Amtech Butorpanol Tartrate Injection	Injectable	10 mg/ml	Same as Torbugesic
Repressor-E	Injectable	10 mg/ml	Same as Torbugesic
Butorphanol EQ	Injectable	10 mg/ml	Same as Torbugesic

1.2 If the answer 1.1 is "no", is there other legitimate use of the substance? N/A

1.3 If there is legitimate use of the substance, how is the substance supplied? (Imported/Manufactured in the country)

Data gathered from the U.S. Drug Enforcement Administration (DEA) Import Declarations from January 1, 2003 through November 8, 2005 indicate that the following quantities of butorphanol were imported into the United States:

Total Butorphanol Imports:

2003: 51,814.88 grams
2004: 39,004.64 grams
2005: 19,024.11 grams (as of November 8, 2005)

Additional details about the amounts of butorphanol imported and the countries of its origin are shown in the table below.

Imports (rounded to the nearest whole gram) of Butorphanol (2003-2005*)

Country	*2003*	*2004*	*2005**

Australia	48	44	-
Canada	9,255	9,672	10,353
Czechoslovakia	23,338	22,429	3,503
Hong Kong	42	17	17
Netherlands	17,238	4,875	3,079
United Kingdom	1,884	1,968	2,071

* Data through November 8, 2005

Data gathered from DEA Export Declarations from January 1, 2003 through November 8, 2005 indicate that the following quantities of butorphanol were exported from the United States:

Total Butorphanol Exports:

2003: 441,986.37 grams
2004: 37,374.66 grams
2005: 16,183.61 grams (as of November 8, 2005)

Additional details about the amounts of butorphanol exported and the countries of its destination are shown in the table below.

Exports (rounded to the nearest gram) of Butorphanol

Country	*2003*	*2004*	*2005**
Argentina (ARG)	172	34	50
Aruba (ARU)	<1	-	-
Australia (AUL)	890	372	539
Bahrain (BAH)	-	4	28
Bermuda (BER)	-	6	1
Belgium (BZE)	2	1	2
Brazil (BRA)	200	-	200
Canada (CAN)	155,608	23,156	5,297
Chile (CHI)	60,628	9	-
Czech Republic (CZE)	201	64	-
Denmark (DEN)	899	-	747
Estonia (EST)	31	-	22
Finland (FIN)	-	-	<1
France (FRA)	-	5	<1
Germany (GER)	1	<1	<1
Guatemala (GUA)	-	4	3
Hong Kong (HOK)	<1	-	-
India (IND)	-	<1	-
Ireland (IRE)	301	468	44
Israel (ISR)	252	22	25
Italy (ITA)	4,815	4,831	3,442
Japan (JPN)	<1	1,034	162
Kuwait (KUW)	<1	-	-
Macao (MAC)	-	-	6
Malaysia (MAL)	-	2	2
Namibia (NAM)	5	6	15
Netherlands (NET)	-	23	-
New Zealand (NZE)	<1	-	<1
Pakistan (PAK)	150	138	-

Panama (PAN)	207,511	-	-
Republic of Serbia (ROS)	<1	-	-
Republic of Korea (ROK)	-	<1	-
Singapore (SIN)	2,263	8	21
South Africa (SAF)	57	36	35
Spain (SPA)	2,878	4,604	4,863
Saint Kitts and Nevis (STK)	75	7	1
Slovenia (SVN)	40	-	50
Sweden (SWE)	240	600	600
Switzerland (SWI)	<1	-	-
Taiwan (TWN)	-	<1	-
United Arab Emirates (UAE)	10	2	12
United Kingdom (UK)	4,752	1,936	6
Venezuela (VEN)	-	-	10

* Data through November 8, 2005.

2. ABUSE OF THE SUBSTANCE

2.1 Is the substance abused or misused in your country? Yes

2.2 If "yes", any information on the extent of abuse?

Abuse of butorphanol products has been documented since its control under the CSA.

The table below shows AERS terms related to abuse and dependence received by the FDA MedWatch system for butorphanol. The reports cover the period from approval of the injectable product in 1978, to approval of the nasal product in 1992, to the year of CSA scheduling in 1997, and finally to November 2005.

COUNTS OF U.S AERS REPORTS FOR ABUSE TERMS FOR WHO QUESTIONNAIRE *TIME-PERIODS FOR BUTORPHANOL*

Administration route	All Butorphanol Products			Nasal Spray Products			Injection Products		
Number of reports[1]	N=4482			N=3574[2]			N=362[2]		
Years reports were received	1978-1991	1992-1996	1997-2005[3]	1978-1991	1992-1996	1997-2005	1978-1991	1992-1996	1997-2005
Number of reports	N=69	N=525	N=3894	N=0	N=475	N=3099	N=14	N=16	N=332
Drug withdrawal syndrome	11	40	278		34	257	3	3	89
Drug tolerance			1			1			
Overdoses									
Intentional overdose	6	1	6			4	1	1	
Overdose	6	20	33		16	23	1		13
Accidental overdose	2	6	10		5	7	1		2
Multiple drug overdose			2			1			1
Substance-Related Disorders									
Dependence			1349			944			199
Drug Dependence	57	494	2390		452	2030	9	12	123
Polysubstance abuse			2			2			

[1]one report may contain more than one preferred term

[2]not all butorphanol reports had a known administration route, as determined via Standard AERS reports.

[3]up to November, 2005

DISCLAIMER FOR STANDARD AERS REPORTS

The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Hence, when considering these figures, it should be realized that accumulated case reports cannot be used to calculate incidence or estimates of drug risk for a particular product, as reporting of adverse events is a voluntary process, and underreporting exists. Further, because of the multiple factors which influence reporting, comparisons of drug safety cannot be made from this data. Some of these factors include the length of time a drug is marketed, the market share, size and sophistication of the sales force, publicity about an adverse reaction and regulatory actions. It should also be noted that in some of these cases, the reported clinical data was incomplete, and there is no certainty that these drugs caused the reported reactions. A given reaction may actually have been due to an underlying disease process or to another coincidental factor. Further, this data was generated using computer printouts, and some of the numbers may reflect duplicates.

In 2004, the HHS Substance Abuse and Mental Health Services (SAMHSA) Administration Survey on Drug Use and Health (NSDUH[1]) reported that approximately 155,000 (0.1 percent) of persons aged 12 or older have used butorphanol (as Stadol) nonmedically in their lifetime.

The Drug Abuse Warning Network[2] (DAWN) collects data on drug-related emergency department (ED) visits from a nationally representative sample of hospitals in the United States and a selection of U.S. metropolitan areas Major changes were introduced to DAWN in 2003, including changes in the case definition, case types, data collection methodology and sample. Because of the many changes introduced in 2003, the most recent estimates available from DAWN are for the second half of the year (6 months) only and pertain to the coterminous U.S. only. Also because of the changes, comparisons cannot be made with any estimates from old DAWN (i.e., prior to 2002). However, there were insufficient data to produce reliable estimates about ED visits involving the misuse/abuse of butorphanol in the second half of 2003 in the United States.

The previous version of the Drug Abuse Warning Network ("old" DAWN) collected data on all drugs mentioned in drug abuse-related ED visits. The final year of old DAWN was 2002. According to the "old" DAWN, in 1994, following the marketing approval of butorphanol nasal spray, there were 35 drug abuse-related emergency room visits involving butorphanol. In 1996, butorphanol was mentioned in 239 drug abuse-related ED visits in the United States. Following the control of butorphanol in Schedule IV of the Controlled Substances Act (CSA), butorphanol involved drug abuse-related ED visits declined to 19 in 1998, but estimates during the subsequent period of 1999 through 2002 were too unreliable for publication.

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[1] The National Survey on Drug Use and Health (NSDUH) is an annual survey of the civilian, noninstitutionalized population of the United States aged 12 years old or older. Conducted by the Federal Government since 1971, the survey collects data by administering questionnaires to a representative sample of the population through face-to-face interviews at their places of residence. NHSDA presents national, state and sub-state estimates of rates of use, numbers of users, and other measures related to illicit drugs, alcohol, and tobacco products. Measures related to mental health problems also are presented, including data on the co-occurrence of substance use and mental health problems, and new data on depression among youths and adults.

NSDUH is the primary source of statistical information on the use of illegal drugs by the U.S. population. The survey is sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA) of the U.S. Department of Health and Human Services and is planned and managed by SAMHSA's Office of Applied Studies (OAS). More information about NSDUH is available at: http://www.oas.samhsa.gov/nsduh.htm

[2] The Drug Abuse Warning Network (DAWN) is a national public health surveillance system that monitors drug-related morbidity and mortality. Data from DAWN are used to measure the health consequences of drug misuse and abuse as they manifest in ED visits and deaths in communities and the Nation. DAWN data tend to cover a different and more diverse population than the substance abuse treatment system, and drug data from DAWN are far more detailed than is possible in most other substance abuse data collection systems.

DAWN uses a probability sample of hospitals to produce annual estimates of drug-related emergency department (ED) visits for the United States and for a selection of metropolitan areas. DAWN also produces annual profiles of drug-related deaths that were reviewed by medical examiners or coroners in selected metropolitan areas and States (it is not possible to use DAWN mortality data to produce any national-level information about drug-related deaths). DAWN data are abstracted from a retrospective review of ED medical records and ME case investigation files according to specified case selection criteria. Any ED visit or death related to recent drug use is included in DAWN. Data are collected on all drugs that caused or are related to the ED visit. Information about the source and the form of the drugs is not collected, because previous experience with old DAWN showed that this information was frequently not available in ED medical records.
All types of drugs—prescription, over-the-counter and illicit—are covered. Alcohol is included for adults when it occurs with another drug, and is always included for minors. DAWN's method of classifying drugs was derived from the Multum Lexicon, Copyright © 2005, Multum Information Services, Inc. More information about DAWN is available at: http://dawninfo.samhsa.gov/

Butorphanol (injectable formulation) reports of abuse were infrequent in the first decade after it was approved for marketing in the United States; most likely due to its limited availability outside the hospital setting. However, butorphanol abuse increased following the introduction of butorphanol nasal spray in 1992. The nasal spray produces rapid onset of effects, high blood concentrations and considerable euphoria. In addition, it was widely available by prescription for use outside a hospital setting. Reports provided by the HHS National Institutes of Health (NIH) National Institute on Drug Abuse's (NIDA) Community Epidemiological Work Group (CEWG) documented increasing trends of abuse of butorphanol and other opioids from 1992 to 1995.

2.3 **Any information on the extent of public health or social problems associated with the abuse of the substance (statistics on cases of overdose deaths, dependence, etc.)?**

Individuals with a history of drug abuse, especially opiate-dependence, are at an increased risk for abuse related problems with butorphanol. However, individuals with no prior history of drug abuse have also become dependent on butorphanol. Adverse reactions produced by butorphanol are similar to those produced by other opiate analgesics.

Butorphanol has been shown to produce physical dependence in animals and humans. Chronic butorphanol administration results in physical dependence evidenced by withdrawal symptoms after termination of use. In human subjects, withdrawal symptoms resembling those of opiate withdrawal were observed when butorphanol was discontinued or when an opioid antagonist was administered to individuals who received large doses of butorphanol for several weeks. Higher doses (8 mg) of butorphanol substituted for morphine in morphine-dependent subjects.

3. ILLICIT ACTIVITIES INVOLVING THE SUBSTANCE

3.1 Any information on the nature and extent of illicit activities involving the substance (clandestine manufacture, smuggling, diversion, seizures, etc.)?

History of diversion of butorphanol prior to scheduling: In 1994, HHS/FDA and DEA conducted a survey on the abuse of butorphanol. Officials from the state boards of pharmacy, drug programs, and drug enforcement representatives from over 40 States responded to this survey. Eighty three percent of respondents stated that they were aware of non-medical use, diversion or abuse of Stadol in their State. Fifteen percent of the States had attempted to regulate butorphanol as a controlled substance, and 44 percent of States reported that non-regulatory entities, such as hospitals, nursing homes, and clinics, found it necessary to institute special controls beyond those of normal prescription drugs to limit access to the drug. Of the States that responded, 74 percent reported that the nasal spray was abused and 52 percent reported that an injectable product was abused. Approximately 60 percent of the States cited that the drug's source was from over-prescribing, 55 percent from forged or altered prescriptions and 6 percent from "street purchases". Twenty-five percent of the States were aware of excessive prescription refill data from health insurance payment plans. Forty eight percent of the States were aware of thefts of Stadol and 11 percent of States reported product tampering. This survey revealed incidences of retail and hospital pharmacy thefts, forged and altered prescriptions, improper prescribing and inappropriate dispensing, doctor shopping, escalating use, requests for early refills, and drug seeking. These abusers were found in urban, suburban, and rural communities. Many States responded to butorphanol abuse problems by placing it under state control. Based on the evidence of significant abuse of butorphanol, the U.S. Federal government controlled butorphanol in Schedule IV of the CSA in 1997.

Diversion of butorphanol after control in schedule IV: According to the System to Retrieve

Information from Drug Evidence (STRIDE[3]), a DEA database to collect drug analysis results from DEA and other federal laboratories systematically, butorphanol drug items analyzed from 2000 to 2004 ranged from 1 to 5 per year (see table below).

STRIDE Data for Butorphanol (2000 - 2005*)

	2000	*2001*	*2002*	*2003*	*2004*	*2005**	*Total*
Number of Exhibits	2	1	2	5	2	3	15

* Data through November 15, 2005

According to the National Forensic Laboratory Information System (NFLIS[4]), a DEA sponsored project to collect drug analyses results from state and local forensic laboratories systematically, butorphanol drug items analyzed from 2000 to 2004 ranged from 6 to 13 per year (see table below). During this period butorphanol prescriptions (IMS Health) decreased from about 930,000 to 600,000.

NFLIS Data for Butorphanol (2000 - 2005*)

	2000	*2001*	*2002*	*2003*	*2004*	*2005**	*Total*
Number of Exhibits	9	6	12	13	7	7	54

* Data through November 15, 2005

4. IMPACT OF SCHEDULING

4.1 If butorphanol is placed under international control, do you think that its availability for medical use will be affected? No

In the United States, butorphanol is controlled in Schedule IV of the CSA. International control of butorphanol in Schedule IV of the Psychotropic Convention would be consistent with U.S. control and would not require the rescheduling of butorphanol in the U.S.

4.2 If "yes", would the reduction adversely affect the provisions of medical care? N/A

3. System to Retrieve Information on Drug Evidence (STRIDE) is a database that maintains all drug analysis done by the U.S. DEA forensic chemists.

4. National Forensic Laboratory Information System (NFLIS) is a DEA-sponsored project to systematically collect solid dosage drug analyses results from state and local forensic laboratories. Currently 300 state and local forensic laboratories are reporting. This represents about 50 percent of all possible drug exhibits from state and local laboratories across the U.S. An exhibit refers to a single submission for forensic analysis. A case usually contains more than one exhibit. An exhibit is not limited to a single unit, but may contain any quantity of bulk material, tablets, capsules, etc. Data can not be trended as the number of laboratories reporting is increasing with time.

2. DRONABINOL (INN) AND ITS STEREO-ISOMERS

1. LEGITIMATE USE OF THE SUBSTANCE

1.1 Is the substance currently registered as a medical product? Yes (See attachment 2, package insert for Marinol)

Dronabinol (Delta-9-Tetrahydrocannabinol, delta-9-THC) is in Schedule I of the U.S. Controlled Substances Act (CSA). Currently, there is one dronabinol-containing approved pharmaceutical product in the United States, Marinol, is controlled in Schedule III of the CSA.

If "yes", since when (year of marketing)?

The dronabinol-containing approved pharmaceutical product, Marinol, was approved for marketing in 1985. In 1999, Marinol was rescheduled from Schedule II to Schedule III of the CSA.

According to the DEA, prescriptions for Marinol increased from about 90,000 in 1999 to about 300,000 in 2004.

Marinol Product

Trade name	*Dosage form*	*Strength(s*	*Indication(s)*
Marinol	Capsule	2.5, 5 and 10 mg	For the treatment of 1) anorexia associated with weight loss in patients with AIDS; and 2) nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments

1.2 If the answer to 1.1 is "no", is there other legitimate use of the substance? N/A

1.3 If there is legitimate use of the substance, how is the substance supplied?

Dronabinol in the product Marinol is available as gelatin capsules in 2.5 mg, 5 mg, and 10 mg strengths.

Dronabinol (delta-9-THC) is manufactured in the United States. The aggregate production quota (the maximum amount that can be legitimately manufactured in the U.S. annually) for dronabinol for years 2003 through 2005 are as follows:

2003: 135.0 kg
2004: 180.0 kg
2005: 312.5 kg

Data gathered from DEA Import Declarations from January 1, 2003 through November 8, 2005 indicate that the following quantities of dronabinol were imported into the U.S.

Total dronabinol imports
2003: 0.02 grams
2004: 0.00 grams
2005: 0.01 grams (as of November 8, 2005)

Data gathered from DEA Export Declarations from January 1, 2003 through November 8,

2005 indicate that the following quantities of dronabinol were exported from the United States.

Total dronabinol exports
2003: 4,307.461 grams
2004: 3,287.103 grams
2005: 2,556.729 grams (as of November 8, 2005)

Additional details about the amounts of dronabinol exported and the countries of its destination are shown in the table below.

Dronabinol exports (rounded to the nearest gram)

Country	*2003*	*2004*	*2005**
Australia (AUL)	-	<1	4.559
Austria (AUS)	3	<1	<1
Brazil (BRA)	-	1	-
Canada (CAN)	1,920	1,938	1,730
Colombia (C0L)	<1	-	1
Czech Republic (CZE)	<1	<1	<1
Denmark (DEN)	150	901	605
France (FRA)	21	10	24
Germany (GER)	444	261	111
Hong Kong (HOK)	<1	<1	-
Hungary (HUN)	<1	-	<1
India (IND)	-	1	-
Ireland (IRE)	-	<1	<1
Italy (ITA)	37	16	19
Japan (JPN)	<1	<1	-
Netherlands (NET)	95	66	-
Norway (NOR)	<1	45	-
Poland (POL)	<1	-	<1
Spain (SPA)	2	<1	<1
Sweden (SWE)	1	11	7
Switzerland (SWI)	33	2	37
Thailand (THA)	-	<1	<1
United Kingdom (UK)	1,451	34	16
Total Export	4,307	3,287	2,557

* Data through November 8, 2005.

2. ABUSE OF THE SUBSTANCE

2.1 Is the substance abused or misused in your country? Yes

2.2 If "yes", any information on the extent of abuse?

Dronabinol, delta-9-tetrahydrocannabinol, is the primary psychoactive constituent that produces the subjective effects associated with marijuana. Marijuana is the most abused substance in the United States and is controlled in Schedule I of the CSA. The pharmaceutical product containing dronabinol, Marinol is associated with low levels of diversion and abuse and is controlled in Schedule III of the CSA.

The U.S. domestic scheduling of delta-9-THC (Schedule I) versus the delta-9-THC containing product Marinol (Schedule III) in the United States is product specific and based on the specific formulation, pharmacokinetic profile, and other factors which mitigate the product's abuse potential. Any future products containing delta-9-THC for medical use would undergo a scientific and medical assessment of abuse liability, as well as safety and effectiveness, will determine the appropriate level of domestic control. Currently, the World Health Organization uses delta-9-THC, dronabinol, and tetrahydrocannabinol (THC) interchangeably without differentiation.

For the purposes of this questionnaire, information is supplied for the sole U.S. pharmaceutical product, Marinol. The abuse potential and scope of the diversion, abuse and public health risks associated with dronabinol may vary significantly depending on the route of administration, the dosage form, and the medical use of the specific dronabinol product. A number of dronabinol-containing products are under development in the United States.

2.3 Any information on the extent of public health or social problems associated with the abuse of the substance (statistics on cases of overdose deaths, dependence, etc.)?

The United States is not aware of any drug-related deaths, drug dependence, or addiction associated with Marinol.

3. ILLICIT ACTIVITIES INVOLVING THE SUBSTANCE

3.1 Any information on the nature and extent of illicit activities involving the substance (clandestine manufacture, smuggling, diversion, seizure, etc.)?

The DEA has only documented a few reports of actual abuse and diversion of Marinol. According to the STRIDE, there were eleven separate exhibits for Marinol abuse and diversion from 1985 through November 15, 2005. These exhibits represented 625 capsules in nine DEA and non-DEA cases.

According to the NFLIS, Marinol drug items analyzed from 2000 to 2004 ranged from two to four per year. From 2000 through November 15, 2005, a total of 16 Marinol exhibits representing 14 cases were reported in the NFLIS data (see table below).

NFLIS Data for Marinol (2000 - 2005*)

	2000	*2001*	*2002*	*2003*	*2004*	*2005**	*Total*
Number of Exhibits	2	4	3	4	2	1	16

* Data through November 15, 2005

3. GAMMA-HYDROXYBUTYRIC ACID (GHB)

1. LEGITIMATE USE OF THE SUBSTANCE

1.1 Is the substance currently registered as a medical product? Yes (See Attachment 3, approved package insert for Xyrem)

If "yes", since when (year of marketing)?

GHB was placed in Schedule I of the CSA in 2000. The GHB product, Xyrem, was placed in Schedule III of the CSA in 2002 when it was approved for marketing.

GHB Product

Trade name	*Dosage form*	*Strength(s)*	*Indication(s)*
Xyrem	Oral solution	500 mg/ml	For reducing excessive daytime sleepiness and cataplexy in patients with narcolepsy

Xyrem is the only GHB-containing product approved for marketing in the United States.

Gamma-Hydroxybutyrate (GHB), also known as sodium oxybate, is a central nervous system depressant that was approved on July 17, 2002. Xyrem, the approved pharmaceutical product, is indicated for reducing excessive daytime sleepiness and cataplexy in patients with narcolepsy and has orphan drug status for this patient population. It is marketed under the Subpart H regulations of the HHS/FDA that requires restricted distribution and a risk management plan. Features of the Xyrem risk management plan include distribution via a centralized pharmacy, required dissemination of educational materials for the prescriber and the patient which explain the risks and proper use of GHB, and the completion of a required prescription form. The patient must indicate that they have read and understand the Xyrem material prior to being provided with drug. The sponsor must periodically report incidences of abuse and diversion to the appropriate agencies.

1.2 If the answer to 1.1 is "no", is there other legitimate use of the substance? N/A

1.3 If there is legitimate use of the substance, how is the substance supplied?

The Aggregate Production Quotas (maximum amounts that can be legitimately manufactured in the U.S. annually) for GHB for 2003 through 2005 are as follows:

2003: 20,000 kg
2004: 8,000 kg
2005: 8,000 kg

Data gathered from the DEA Import/Export Declarations from January 1, 2003 through November 8, 2005 indicate that no GHB was imported into the United States in the past three years and the following quantities of GHB were exported from the United States.

Total GHB Exports

2003: 164.47 kg
2004: 211.47 kg
2005: 1,855.92 kg (as of November 8, 2005)

Additional details about the amounts of GHB exported and the countries of its destination are shown in the table below.

GHB Exports (rounded to the nearest gram) (2003-2005*)

Country	*2003*	*2004*	*2005**
Australia (AUL)	-	-	166
Austria (AUS)	-	-	9
Belgium (BEL)	18,876	2,092	-
Canada (CAN)	106,074	159,987	74,833
Germany (GER)	-	-	1,494
Japan (JPN)	-	41.5	-
Country	*2003*	*2004*	*2005**
Poland (POL)	-	-	8
Thailand (THA)	-	-	8
United Kingdom (UK)	39,519	49,342	1,779,404
Total Exports	164,469	241,462	1,855,923

* Data through November 8, 2005

2. ABUSE OF THE SUBSTANCE

2.1 Is the substance abused or misused in your country? Yes

2.2 If "yes", any information on the extent of abuse?

In addition to its approved indication for treating the symptoms of narcolepsy, GHB is a known drug of abuse. The most recent drug abuse indicators demonstrate that abuse has stabilized and involves GHB of clandestine manufacture primarily and is not the result of diverted pharmaceutical product (Xyrem). Post marketing data for Xyrem have not revealed evidence of abuse of this product. From July 2002 to September 2004, 5,869 patients were registered for Xyrem use. There are five reports submitted to the HHS/FDA from the central pharmacy involving stolen Xyrem bottles. Although GHB is currently controlled, it continues to be abused in the United States, fueled by illicit production in clandestine laboratories and illicit sales by trafficking organizations and internet pharmacies.

Throughout the 1990's, GHB abuse originating from clandestine illicit laboratories escalated. Kits and recipes for making GHB were available for sale over the Internet. Using these kits, GHB was made in small quantities on college campuses and in larger scale by clandestine laboratories using the precursors, GBL and sodium hydroxide (lye). GBL has since been controlled by DEA as a List I chemical precursor. In the United States, GHB is abused by high school and college students, rave party participants, bodybuilders and individuals who use GHB to incapacitate women for the purpose of committing sexual assault. Abuse of GHB has been

associated with central nervous system (CNS) adverse events that include seizures, respiratory depression and profound decreases in level of consciousness, with instances of coma and death. In 1990 and 1997, HHS/FDA issued health warnings about GHB, which was sold as a dietary supplement in health food stores and gymnasiums. HHS/FDA declared GHB a dangerous, unapproved drug after the HHS Center for Disease Control and Prevention (CDC) published a study of toxicity and reported adverse events associated with its use.

The Drug Abuse Warning Network (DAWN) collects data on drug-related emergency department (ED) visits from a nationally representative sample of hospitals in the U.S. and a selection of metropolitan areas. Major changes were introduced to DAWN in 2003, including changes in the case definition, case types, data collection methodology and sample. Because of the many changes introduced in 2003, the most recent estimates available from DAWN are for the second half of the year (6 months) only and pertain to the coterminous U.S. only. Also because of the changes, comparisons cannot be made with any estimates from old DAWN (i.e., prior to 2002).

GHB was involved in 978 drug misuse/abuse emergency department visits (95 percent confidence interval [CI] 523 – 1,433) in the second half of 2003 in the United States.

The previous version of the Drug Abuse Warning Network ("old" DAWN) collected data on all drugs mentioned in drug abuse-related ED visits. The final year of old DAWN was 2002. The estimates from old DAWN of GHB involvement in ED visits from 1995 to 2002 are shown in the table below. Reports of GHB increased from 1995 to 2000, but declined from 2000 to 2002.

Table 3. Estimates of Emergency Department (ED) Visits Involving GHB from "Old DAWN"*: (1995-2002)

Year	*ED Visits*
1995	145
1996	638
1997	762
1998	1,282
1999	3,178
2000[1]	4,969
2001	3,340
2002	3,330

*Source: Substance Abuse and Mental Health Services Administration, Office of Applied Studies, Drug Abuse Warning Network.

[1]GHB was scheduled under the Controlled Substances Act (CSA).

2.3 Any information on the extent of public health or social problems associated with the abuse of the substance (statistics on cases of overdose deaths, dependence, etc.)?

Depending on the dose, GHB can produce drowsiness, dizziness, nausea, visual disturbances, decreased blood pressure and heart rate. GHB alone or in combination with alcohol or other CNS depressants, can cause seizures, respiratory depression, decreased consciousness, and coma. Overdoses usually require emergency medical treatment including intensive care for respiratory depression and coma. GHB toxicity has been described in many scientific case studies and in the 1990 and 1997 HHS/CDC reports. GHB is sometimes mixed with alcohol to intensify its effects, leading to increased respiratory depression and coma. Recent studies and case reports show that chronic GHB use produces psychological and physical dependence and a withdrawal syndrome upon termination of use. Both psychological and physical dependence may contribute to

the continued abuse of GHB.

In a report to the U.S. Attorney General in June 2000, the DEA documented cases of overdose, abuse and trafficking encounters in 46 U.S. States. There were 5,100 reports from poison control centers, hospitals, and other sources, including 69 deaths associated with GHB abuse.

From 1996 through 2000, DEA documented 18 cases in which GHB was used to incapacitate victims to commit sexual assault. These cases were verified by forensic evidence, including GHB in urine, drug samples at the scene, videotapes of the assaults, or admissions from the suspect. GHB has a fast onset of effects and can impair a victim quickly. As a depressant, this drug produces sedation, a loss of consciousness and an inability to recall the events occurring after ingestion including the assault, the assailant, or the events surrounding the physical evidence of an assault. GHB is metabolized quickly in the body and is difficult to detect. Victims may not be aware that they ingested a drug or were sexually assaulted until 8 to12 hours later. In fact, due to the nature of the crime, and because the victim's memory is not intact, there may be little or no physical or toxicological evidence to support the claim that the sexual assault was facilitated by the use of GHB. This makes it very difficult to ascertain the scope and magnitude of the problem. Many GHB sexual assaults may go unreported or unverified. There were 110 additional sexual assaults reports to DEA from hospitals and rape crisis centers. Studies from alleged sexual assault victims found 90 GHB-positive urine samples (ElSohly and Salamone, 1999; Hoffman-La Roche, 2000).

Data from old DAWN indicated that the highest rates for GHB in drug abuse-related ED visits from 1996 to 2002 were for patients 18 to 25 years of age. GHB was often combined with other drugs, especially alcohol. In 2002, 84 percent of the GHB-related visits involved at least one other drug, and alcohol was involved in 64 percent of the ED visits.

Data from poison control centers across the United States suggest that the intentional abuse of GHB and analogue/precursor may be declining but is still associated with significant morbidity. Table 4 provides information on GHB exposures as reported in the Toxic Exposure Surveillance System (TESS) from poison control centers throughout the United States.

Table 4. GHB Exposures Reported by TESS (Toxic Exposure Surveillance System)

	2001	*2002*	*2003*
Total Exposures	1,916	1,386	800
Intentional Exposures	1,205	883	430
Serious Outcome*	363	272	132
Death	6	3	0

* Exposures resulted in continued, long-term disability or medical problem.

Supported by a grant from NIDA to the University of Michigan, Monitoring the Future (MTF) is an annual school-based survey of 8th, 10th and 12th graders attending public and private school in the coterminous United States. Questions on past year use of GHB were added to the MTF survey questionnaire in 2000. The 2005 MTF study finding show that the percent of 12th grade students reporting use of GHB in the past year declined significantly from 2004 to 2005. The annual prevalence (use in the past year) of GHB use has declined significantly in each grade since the peak use year (2000 for 8th graders, 2002-2003 for 10th graders and 2004 for 12th graders).

GHB Abuse Reported by MTF:

	2000	2001	2002	2003	2004	2005
8th Grade	**1.2**	1.1	0.8	0.9	0.7	0.5
10th Grade	1.1	1.0	**1.4**	**1.4**	0.8	0.8
12th Grade	1.9	1.6	1.5	1.4	**2.0**	1.1

Data are expressed as percent of students reporting use during the past year. Peak use year appears in bold print

Two drug abuse indicators, TESS and MTF, show a downward trend from 2001 to 2004 to suggest that abuse of GHB is plateauing or decreasing. As stated previously, indicators also demonstrate that abuse primarily involves GHB of clandestine manufacture and is not the result of diverted pharmaceutical product (Xyrem).

3. ILLICIT ACTIVITIES INVOLVING THE SUBSTANCE

3.1 Any information on the nature and extent of illicit activities involving the substance (clandestine manufacture, smuggling, diversion, seizure, etc.)?

Prior to its control in 2000 under the CSA, DEA documented 1,400 law enforcement cases involving GHB, including clandestine laboratories, forensic analyses, possession, trafficking, driving under the influence cases, and sexual assault reports. In illicit trafficking, GHB is most commonly found in liquid form in vials or small bottles or found as powdered material.

GHB is clandestinely produced using a simple synthesis with available and inexpensive starting materials. It is typically produced in aqueous solutions and is found as a clear liquid. Confiscated samples have been encountered in a variety of containers including vials, water bottles (sometimes disguised as mouthwash or other liquid), plastic bags, milk containers, buckets, and 55-gallon drums. GHB has been seized in quantities ranging from less than one gram to 32 kilograms (powder) and from less than 1 ml to 60 gallons (liquid). Since 1993, abuse, overdose, clandestine manufacture, and trafficking of GHB have been seen in nearly every U.S. State. Part of the reason for its widespread abuse is the proliferation of Internet websites that sold GHB kits and provided information on how to manufacture GHB at home. From 1990 through 2004, DEA received documentation of 212 GHB clandestine laboratories.

The number of GHB clandestine laboratories seized for each year since 1990 is presented in the table below.

GHB Clandestine Laboratory Activity (1990-2004)

Year	*Laboratories*
1990	1
1991	-
1992	1
1993	6
1994	3
1995	8
1996	10
1997	23
1998	67
1999	51
2000[1]	9
2001	12
2002	7
2003	4
2004	10

[1]GHB was scheduled under the CSA.

According to the STRIDE, GHB has been seized in large quantities in powder and liquid form. There were a total of 578 drug exhibits reported in the STRIDE from 1994 through November 15, 2005.

STRIDE Data for GHB (1994 – 2005)

Year	*Number of Cases*	*Number of Exhibits*	*Powder (grams*)*	*Liquid (mls*)*	*Capsules*	*Tablets*
1994	2	2	2	6,688	-	-
1995	7	10	513	3,930	812	-
1996	13	17	1,058	1,754	-	-
1997	16	46	659	23,770	-	-
1998	12	28	124	6,190	-	2
1999	17	40	2,552	3,641	-	-
2000[1]	43	108	21	1,141,818	1	-
2001	40	85	86,352	100,520	-	-
2002	40	81	383	78,070	-	-
2003	30	62	18,737	133,444	-	-
2004	40	77	< 1	34,994	-	-
2005**	11	22	< 1	70,885	-	-
TOTAL	271	578	110,402	1,605,703	813	2

* Data rounded to the nearest whole unit

** Data through November 15, 2005.

[1]GHB was scheduled under the CSA.

According to the NFLIS, there were a total of 1,842 GHB exhibits from 2000 through November 15, 2005.

NFLIS Data for GHB (2000 – 2005)

Year	*Number of Exhibits*
2000[1]	402
2001	254
2002	392
2003	302
2004	292
2005*	200

* Data through November 15, 2005; [1] GHB was scheduled under the CSA

The table below provides additional data on selected federal GHB cases reported to STRIDE (2003 to November 30, 2005). These cases are provided to demonstrate that some GHB cases involve significant amounts of seized GHB. These data also indicate that illicit activities with GHB continue to be a serious problem in the U.S despite the various regulatory controls and enhanced penalties that have been placed on both the substance and the product.

Significant Federal GHB Cases

Year Seized and Case Location	*Number of Drug Exhibits*	*Powder (grams)*	*Liquid mls)*	*Comments*
2003 New York, NY	5	17,810	37,632	One purchase of 17,360 ml for $2500; Another purchase of 17,810 ml for $2500
2003 Lighthouse Point, FL	7	-	32,655	
2004 Dallas, TX	11	-	4,207	
2004 Plano, TX	1	-	3,780	A FBI case. Purchase price was $1500
2004 Grand Prairie, TX	2	-	2,070	
2005 Tampa, FL	6	-	49,746	A DEA and State & Local case.
2005 Tampa, FL	4	-	15,001	One purchase of 3,800 mls for $900; Other purchases included 3,850 ml for $2500 and 3,719 mls for $2500.

4. IMPACT OF TRANSFER TO SCHEDULE II or III OF THE CONVENTION ON PSYCHOTROPIC SUBSTANCES, 1971, ON MEDICAL AVAILABILITY

4.1 If gamma-hydroxybutyric acid is transferred from Schedule IV of the Convention on Psychotropic Substances, 1971, to either Schedule II or III of the Convention on Psychotropic Substances, do you think that its availability for medical use will be affected? No

The U.S. would not need to alter the control of GHB should it be transferred to Schedule II or III of the Psychotropic Convention.

4.2 If "yes", how do you think the transfer will impact its medical availability? N/A

4. KETAMINE (INN)

1. LEGITIMATE USE OF THE SUBSTANCE

1.1 Is the substance currently registered as a medical product? Yes (See attachment 4, package insert for Ketasert)

If "yes", since when (year of marketing)?

Ketamine has been marketed in the U.S. since 1970 and was placed in Schedule III of the Controlled Substances Act (CSA) in 1999.

Ketamine Products Approved For use in Humans

Trade name	*Dosage form*	*Strength(s)*	*Indication(s)*
Ketalar	Injectable solution	10, 50 and 100 mg/ml	Used for restraint or as the sole anesthetic agent in diagnostic or minor, brief surgical procedures that not require skeletal muscle relaxation in humans
Ketamine hydrochloride	Injectable	50, 100 mg base/ml	Used for restraint or as the sole anesthetic agent in diagnostic or minor, brief surgical procedures that not require skeletal muscle relaxation in humans

Ketamine Products Approved For Use in Animals

Trade Name	*Dosage form*	*Strength(s)*	*Indication(s)*
Ketaset	Injectable solution	100 mg base/ml	Used for restraint or as the sole anesthetic agent in diagnostic or minor, brief surgical procedures that do not require skeletal muscle relaxation in cats, and nonhuman primates
Vetalar	Injectable solution	100 mg base/ml	Same as Ketaset
Vetaket	Injectable solution	100 mg base/ml	Same as Ketaset
Ketaject	Injectable solution	100 mg base/ml	Same as Ketaset
Ketamine hydrochloride injection	Injectable solution	100 mg base/ml	Same as Ketaset
Ketaved	Injectable solution	100 mg base/ml	Same as Ketaset
Amtech Ketamine Hydrochloride Injection USP	Injectable solution	100 mg base/ml	Same as Ketaset
Vetus Keta-Thesia	Injectable solution	100 mg base/ml	Same as Ketaset

In 2004, there were approximately 11,000 prescriptions dispensed for ketamine products (DEA - IMS Health). It is important to note ketamine use in emergency care and veterinary practice by licensed personnel is extensive and would generally not require a prescription for use in these arenas.

1.2 If the answer to 1.1 is "no", is there other legitimate use of the substance? N/A

1.3 If there is legitimate use of the substance, how is the substance supplied? (Imported / Manufactured in the country)

Bulk ketamine is not manufactured domestically. It is imported into the United States and manufactured into dosage forms by various pharmaceutical companies. Data gathered from the DEA Import Declarations from January 1, 2003 through November 8, 2005 indicate that the following quantities of ketamine were imported into the United States.

Total Ketamine Imports
2003: 1,180,092.00 grams
2004: 3,257,808.44 grams
2005: 2,132,639.70 grams (as of November 8, 2005)

Additional details about the amounts of ketamine imported and the countries of its origin are shown in the table below.

U.S. Imports (rounded to the nearest gram) for Ketamine (2003-2005*)

Country	*2003*	*2004*	*2005**
Germany (GER)	1,068,092	2,575,840	2,045,370
France (FRA)	87,000	304,500	87,000
China (CPR)	2,500	374,000	<10
United Kingdom (UK)	-	-	261
Belgium (BEL)	-	3,468	-
Canada (CAN)	-	<10	-

*Data through November 8, 2005

Data gathered from DEA Export Declarations from January 1, 2003 through November 8, 2005 indicate that the following quantities of ketamine were legitimately exported from the United States.

Total Ketamine Exports
2003: 463,804.519 grams
2004: 142,098.897 grams
2005: 997,402.508 grams (as of November 8, 2005)

Additional details about the amounts of ketamine exported and the countries of its destination are shown in the table below.

U.S. Exports (rounded to the nearest gram) of Ketamine (2003-2005*)

Country	*2003*	*2004*	*2005**
Argentina (ARG)	-	<10	<10
Australia (AUL)	51,842	1,368	91,531
Austria (AUS)	-	-	<10
Bahrain (BAH)	-	-	300
Country	*2003*	*2004*	*2005**
Bahamas (BHA)	-	125	-
Belgium (BZE)	300	-	30
Brazil (BRA)	5,400	27,700	<10
Brunei Darussalam (BRU)	-	-	<10

Canada (CAN)	19,311	28,444	35,513
Colombia (COL)	-	<10	-
Czech Republic (CZE)	<10	-	-
Denmark (DEN)	-	-	13
El Salvador (ELS)	<10	-	-
Finland (FIN)	<10	<10	-
France (FRA)	4,916	17	122
Germany (GER)	40	68	16
Greece (GRE)	<10	1,944	<10
Guatemala (GUA)	-	20	580
Hong Kong (HOK)	-	<10	<10
Hungary (HUN)	<10	10	<10
Indonesia (INS)	<10	<10	4,350
Ireland (IRE)	132,849	8,967	-
Israel (ISR)	20,017	15,231	22,611
Italy (ITA)	56	56	95
Japan (JPN)	174,064	1,507	522,832
Madagascar (MAG)	50	-	-
Mongolia (MON)	-	-	685
Netherlands (NET)	-	<10	-
Norway (NOR)	<10	<10	<10
Paraguay (PAR)	-	-	<10
Poland (POL)	-	13	-
Portugal (POR)	-	<10	<10
Republic of Korea (ROK)	13,072	<10	27,850
Saudi Arabia (SAU)	900	783	500
Singapore (SIN)	-	<10	-
Spain (SPA)	88	16,264	14,691
Saint Kitts and Nevis (STK)	500	1,030	110
Sweden (SWE)	0.00	10.437	0.00
Switzerland (SWI)	15	12	-
Thailand (THA)	<10	<10	<10
Turkey (TUR)	1,2180	-	24,360
Taiwan (TWN)	8,719	20	8,759
United Arab Emirates (UAE)	500	-	-
United Kingdom (UK)	18,612	7,444	230,733
Venezuela (VEN)	500	40,000	11,701

* Data through November 8, 2005.

2. ABUSE OF THE SUBSTANCE

2.1 Is the substance abused or misused in your country? Yes

2.2 If "yes", any information on the extent of abuse?

Soon after its introduction into the U.S. market, ketamine was discovered and abused by individuals interested in psychedelic drugs, and those who had ready access to the drug, such as anesthesiologists and veterinarians. In the mid 1990s, ketamine was introduced to the rave scene. Common names used for ketamine include "Special K", or "K", and was described as

"the new Ecstasy," and "psychedelic heroin." The liquid from ketamine products is evaporated and the resulting powder is snorted. DEA began receiving reports of veterinary clinic robberies directed at ketamine at the same time teenagers and young adults were found selling the drug, under its influence or having it in their possession. Ketamine was placed into Schedule III of the Controlled Substance Act on August 12, 1999.

SAMHSA's Drug Abuse Warning Network (DAWN) collects data on drug-related emergency department (ED) visits from a nationally representative sample of hospitals in the U.S. and a selection of metropolitan areas. Major changes were introduced to DAWN in 2003, including changes in the case definition, case types, data collection methodology and sample. Because of the many changes introduced in 2003, the most recent estimates available from DAWN are for the second half of the year (6 months) only and pertain to the coterminous U.S. only. In the second half of 2003, ketamine was involved in 63 drug misuse/abuse-related ED visits.

According to the FDA adverse events reporting system, a total of 57 ketamine abuse-related adverse events have been reported by 46 individuals from 1970 through November, 2005. The majority (79 percent) of these events are related to ketamine dependence, abuse and overdoses.

2.3 Any information on the extent of public health or social problems associated with the abuse of the substance (statistics on cases of overdose deaths, dependence, etc.)?

Ketamine can be taken orally, smoked, snorted, or injected. If snorted, the most common route of administration, a low dose (approximately 50 mg) produces effects in 5 to 10 minutes similar to those produced by Quaalude (methaqualone). Higher doses (approximately 100 to 150 mg) produce intense alterations in mood, perception, thinking, body awareness, and self-control. Reports of hallucinations, personal and creative problem solving, and out-of-body-near-death experiences have occurred during this experience which is described as a "K-hole." Tolerance develops after repeat administration, requiring an increase in the frequency of administration and dose in order to attain the desired state of mind

In a report to the U.S. Attorney General in June 2000, DEA documented three cases of sexual assault where ketamine was used or alleged to be used to commit a sexual assault. The extent to which ketamine may be used for this purpose is unknown. Ketamine is not tested on a routine drug screen. Ketamine in body fluids must be specifically tested in order to detect its presence. Roughly two hours after administration, ketamine and its metabolite cannot be detected in blood or newly formed urine.

Supported by a grant from NIDA to the University of Michigan, Monitoring the Future (MTF) is an annual school-based survey of 8th, 10th and 12th graders attending public and private school in the coterminous United States. Questions on past year use of Ketamine were added to the MTF survey questionnaire in 2000. There was no statistically significant change in reporting of the use of Ketamine in the past year among 8th, 10th or 12th graders from 2004 to 2005. However, the findings from the 2005 survey indicate that annual prevalence of Ketamine use has declined significantly since 2001 in each grade surveyed.

Ketamine Abuse Reported by MTF**:**

8th Grade	**1.6**	1.3	1.3	1.1	0.9	0.6
10th Grade	2.1	2.1	**2.2**	1.9	1.3	1.0
12th Grade	2.5	2.5	**2.6**	2.1	1.9	1.6

Data are expressed as percent of students reporting use during the past year. Peak use year appears in bold print

3. ILLICIT ACTIVITIES INVOLVING THE SUBSTANCE

3.1 Any information on the nature and extent of illicit activities involving the substance (clandestine manufacture, smuggling, diversion, seizure, etc.)?

Since 1994 DEA has received more than 731 reports of the sale and/or use of the drug by minors in schools, on college campuses, at nightclubs and rave dances. Individuals under the influence of ketamine have been associated with incidents of public intoxication and improper operation of motor vehicles. Initially, burglaries of veterinary clinics were the primary source of the drug. Currently, diversion of legitimate shipments and smuggling provide significant amounts of ketamine to the illicit market. There is no evidence of clandestine manufacture. The complex and exacting synthesis does not appear to be within the expertise of most clandestine laboratory operators.

Roughly two metric tons of legitimate drug are available in the United States annually, of which ninety percent is used in veterinary products. The residue from the evaporated liquid pharmaceutical products can be ground to a powder that is distributed in small Ziplock bags, "personal use" bottles, capsules, and/or paper, glassine or aluminum "folds" for illicit use. Tablets, while common in Europe and Australia, are rarely encountered in the United States with the exception of one large seizure of about 40,000 tablets in 2001. From a sample of 170 Ziplock bags purchased or obtained in multi-unit seizures, the average weight of powder contained in one small Ziplock bag was 141 milligrams, with a range of 50 to 371 milligrams. A $20 bag of ketamine is reported to provide at least enough to achieve "K-land".

In 2001, a Mexican drug ring was identified as a primary supplier of illicit ketamine. This gang smuggled thousands of vials of pharmaceutical ketamine from Mexico into the United States. The bulk ketamine was imported from China to Mexico, manufactured into dosage forms in Mexico, and then diverted into the United States by concealing it in hidden compartments in cars. Once in the United States, the ketamine was transported to various storage lockers. U.S. customers purchased the ketamine products over the Internet. In September 2002, U.S. DEA and Mexican law enforcement dismantled this drug ring in Panama, Mexico. Three of the key members of this drug ring were arrested. About 250,000 vials of ketamine were seized along with 400 kg of ketamine powder.

According to the STRIDE, a significant amount of ketamine is still being encountered on the illicit market. The table below provides information from DEA and other federal laboratories regarding ketamine cases, exhibits and seized material.

STRIDE Data for Ketamine (2000 – 2005*)

Year	*Number of Cases*	*Number of Exhibits*	*Powder (grams)*	*Liquid (mls)*	*Tablets*	*Capsules*

2000	85	173	11,223	184,908	5	-
2001	139	317	49,225	563,812	40,073	-
2002	130	264	11,462	305,904	4,075	-
2003	85	173	21,415	25,907	23	-
2004	63	154	5,957	90,962	106	-
2005*	39	80	58,480	57,102	0	1
TOTAL	541	1,161	157,764	1,228,596	44,282	1

* Data through November 15, 2005

In 2004 and 2005, a number of cases reported in STRIDE involved significant seizures of ketamine. This data is summarized in the following two tables.

Significant Ketamine Seizures (STRIDE Data) in 2004

Date	*Location*	*Amount Seized*	*Form*	*Dosage Units*	*Comments*
01/2004	Los Angeles, CA	2,000 ml	Liquid	2,400	
02/2004	San Ysidro, CA	5,198 ml	Liquid	58,737	
02/2004	San Ysidro, CA	5,198 ml	Liquid	60,817	
02/2004	San Ysidro, CA	5,198 ml	Liquid	57,698	
01./2004	San Ysidro, CA	2,200 ml	Liquid	25,080	Seized by U.S. Customs
02/2004	Taylorsville, UT	100	Tablets	100	Tablets contained ketamine, methamphetamine, and caffeine
03/2004	Levittown, PA	1,102 gm	Powder		
09/2004	San Salvador, El Salvador	56,781 ml	Liquid	67,483	
10/2004	Las Cruces, NM	5,089 gm	Powder		
11/2004	San Ysidro, CA	4,010 ml	Liquid	46,516	Vial labeled "Anesket Ketamina 1000 mg/ml Solucion Inyectable Contenido Net 10 ml"
11/2004	San Ysidro, CA	1,000 ml	Liquid	11,400	Vial labeled "Ketamina 1 G Cheminova USO Veterinario Solucion Injectable Ketamina (CL Orhidrato) 1.152 G Vehículo C.S.P. 10 ml"

Significant Ketamine Seizures (STRIDE Data) in 2005*

Date	*Location*	*Amount Seized*	*Form*	*Dosage Units*	*Comments*
01/2005	New York, NY	3,675 ml	Liquid	18,375	U.S. Customs seized this at J.F.K. Intl. Airport
02/2005	San Ysidro, CA	9,240 ml	Liquid	53,592	Seized by U.S. Customs
02/2005	San Gabriel, CA	2,570 ml	Liquid	27,499	Cheminova brand ketamine (1 gram of ketamine base in 10 ml of vehicle.)

04/2005	Alhambra, CA	2,215 ml	Liquid	25,030	212 vials seized. The vials were labeled "Ketamin 10 percent INY 12 Frascos DE 10 ml Dutch Farm Veterinary Pharamceutic ALS Formula CADA ML Contiene Ketamina (Clorhidrasto)
04/2005	Philadelphia, PA	48,638 gm	Powder	4,717,886	
04/2005	Philadelphia, PA	920 gm	Powder	574,240	
08/2005	Corona, CA	4490 ml	Liquid	49,839	Vials labeled "Ketamina 1G Cheminova Contenido Neto 10 ml Ketam Ina (Chloridrato) 1G Vehicyuko C.S.P. 19ml.
08/2005	Corona, CA	4,500 ml	Liquid	50,400	Vials labeled 'Anesket Ketamina 100mg/10ml Solution Inyectabel E. LOTE No: C035319 FECHA 08 MAR 2007"
08/2005	Mayaguez, Puerto Rico	22,870 ml	Liquid		Joint DEA/U.S. Custom seizure
09/2005	Irvine, CA	1,000 ml	Liquid	11,500	Amber vials labeled " Ketamina 1G Chemonova Solucion Inyectable Formula: ketamina (Clorhihdrato): 1G Vehi"
09/2005	Irvine, CA	1,000 ml	Liquid	11,500	Clear vials labeled "Anesket Ketamina 1000mg/ml L, Solucion Inyectable, Formula: … Clorhidrato.
09/2005	Irvine, CA	70 ml	Liquid	798	Vials labeled "Anesket, Ketamina 100mg/10ml. Solucion Inyectable…Clorhidrato De Ket Amina Equivalente a 100 mg De Ketamina, Vehículo"
09/2005	Irvine, CA	240 ml	Liquid	2736	Vials labeled "Ketamina 1G, Cheminova Formula: Ketamina (Clorhidrato)… 1G Vehículo C. D.P. 10ml, LOTE No 05-02, Fecha De Caducidad Jul

*Data through November 2005

According to the NFLIS, ketamine drug exhibits ranged from 565 to 1501 per year during 2001 - 2004. Data obtained for the period of 2001-2005 from NFLIS are shown in the table below.

NFLIS Data for Ketamine from State and Local Laboratories (2001 – 2005)

Year	*Cases*	*Exhibits*
2001	882	1,089
2002	1,201	1,501
2003	640	752
2004	478	565
2005*	220	265

*Data through November 15, 2005

U.S. Customs Services data indicate that ketamine is being illicitly imported into the United States from several foreign countries. The table below identifies the countries of origin of ketamine seized by U.S. Customs officials.

U.S. Customs Services Data: Source Countries for Ketamine Smuggling

Year	*Countries*
2001	Canada , China (Mainland), India, Mexico, Paraguay, Peru, Philippines
2002	Japan, Mexico, Panama, Peru, Philippines, Romania
2003	Argentina, Canada, Dominican Republic, Ecuador, India, Mexico, Pakistan
2004	Canada, Dominican Republic, India, Mexico, Pakistan, Peru, Philippines, United Kingdom, United States, Uruguay, Zimbabwe

In 2001, the International Criminal Police Organization (INTERPOL) conducted a survey with all members of the National Central Bureau (NCBs) on the control status, licit use, and abuse of ketamine. The U.S. response to the survey was provided by the DEA. At the time of the survey, DEA reported that the abuse of ketamine in the United States was widespread as indicated by data from DAWN[5]; the National Institute on Drug Abuse's Monitoring the Future Survey, STRIDE and NFLIS databases. These data indicated that ketamine abuse posed a significant threat to the public health and justified the domestic control of ketamine. In response to the question "is there a history of abuse or diversion", nine other countries and special administrative regions, namely Australia, Canada, China (Macau), China (Hong Kong), Finland, Ireland, New Zealand, Norway, United Kingdom, reported incidences of ketamine abuse.

4. IMPACT OF SCHEDULING

4.1 If ketamine is placed under international control, do you think that its availability for medical use will be affected? No

Ketamine is currently controlled in Schedule III of the Controlled Substances Act (CSA). International Control would not affect the medical use of this drug in the United States and may significantly reduce the amount of ketamine that is illicitly shipped into the U.S.

4.2 If "yes", how do you think the transfer will impact its medical availability? N/A

5 In 2002, ketamine was mentioned in 260 drug abuse-related ED visits based on historical estimates from old DAWN.

5. KHAT (CATHA EDULIS Forsk.)

1. LEGITIMATE USE OF THE SUBSTANCE

1.1 Is the substance currently registered as a medical product? No

1.2 If the answer to 1.1 is "no", is there other legitimate use of the substance?

Khat has no legitimate medical use in the United States. Cathinone and cathine, the active constituents of khat, are controlled in Schedules I and IV of the Controlled Substances Act (CSA), respectively. In the United States, khat is subject to Schedule I controls when it contains cathinone. When it contains only cathine, it is subject to Schedule IV controls.

2. ABUSE OF THE SUBSTANCE

2.1 Is the substance abused or misused in your country? Yes

2.2 If "yes", any information on the extent of abuse?

In the United States, immigrants from the countries of Somalia, Ethiopia, and Yemen are the main users of Khat. These individuals use it in casual settings or religious ceremonies. Highest abuse of khat is found in cities with a sizable immigrant population from these countries. These cities include Boston, MA; Columbus, OH; Dallas, TX; Detroit, MI; Kansas City, KS; Los Angeles, CA; Minneapolis, MN; Nashville, TN; New York, NY; and Washington DC. Law enforcement reports indicate that individuals outside of these areas have begun abusing this substance. Khat has long been a substitute for alcohol among Muslims. Many Muslims, including Somalis, use khat during the religious month of Ramadan.

Khat is typically ingested by chewing the leaves. Dried khat leaves can be brewed in tea or cooked. Abusers report that the effects of khat are similar but less intense than effects caused by cocaine or methamphetamine.

2.3 Any information on the extent of public health or social problems associated with the abuse of the substance (statistics on cases of overdose deaths, dependence, etc.)?

According to historical data from the old DAWN, from 1995 to 2002 there was only one drug abuse-related emergency department visit in the Nation that involved khat (in 1999). The Toxic Exposure Surveillance System (TESS, poison control data) had no reports of exposures involving khat from 2001 to 2003. However, evidence published in the scientific literature indicates that khat abuse can lead to adverse effects on the cardiovascular and central nervous system.

3. ILLICIT ACTIVITIES INVOLVING THE SUBSTANCE

3.1 Any information on the nature and extent of illicit activities involving the substance (clandestine manufacture, smuggling, diversion, seizure, etc.)?

Seizure data indicate that the availability of khat is increasing in the United States. According to Federal-wide Drug Seizure System (FDSS) data, law enforcement seizures of khat increased from 14 metric tons in 1995 to 37 metric tons in 2001. State and local law

enforcement officials frequently seize kilogram quantities of khat. Most khat seized in the United States have been from immigrants from the countries of Somalia, Ethiopia, Yemen, Eritrea, and others where khat use is common.

U.S. law enforcement officials indicate that a large number of khat seizures occur during the month of Ramadan. For example, from November 5 to December 4, 2002, U.S. Custom Service (USCS) officials seized nearly 3000 kilograms of khat from airports in CA, IL, KY, MN, NY and TN. Khat is frequently advertised openly on signs in ethnic restaurants, bars, grocery stores, and smoke shops. Signs often are printed in the native language of the store owner. Khat generally sells for $300 to $400 per kilogram or $28 to $50 per bundle (40 leafed twigs measuring 12 to 15 inches in length).

In 2004, Kansas City Police Department (KCPD) reported the emergence of a new form of khat within the Somali community. Graba, a dried form of khat that is similar in appearance to marijuana, was seized by KCPD. Graba is produced in Ethiopia and is commonly dried before it is transported into the United States. From two separate incidents in January 2004, KCPD officers seized 13.2 pounds of graba from an Ethiopian national and 38 grams from a Somali national. According to the National Drug Intelligence Center, Somali and Yemen independent dealers are distributing khat in Ann Arbor, Detroit, Lansing and Ypsilanti, MI; Columbus, OH; Kansas City MO; and Minneapolis/St. Paul, MN.

Because of limited shelf life of hydrated khat, it needs to be transported quickly to the intended market. Thus the shipment by air is the most common method of transport. Khat is primarily transported through the United Kingdom and Canada via package delivery services and to a lesser extent by couriers aboard commercial aircraft. It is often listed as Abyssinian or African tea, African salad, molokheya (an Egyptian vegetable), perishable lettuce or fresh vegetables, tobacco leaves, and herbs. To maintain freshness during transport, khat is frequently wrapped in plastic bags, banana leaves, or news papers and sprinkled with water.

There was one incidence of khat cultivation in Salinas, CA. An individual of Middle-Eastern descent used sophisticated irrigation techniques to cultivate khat and gained approximately $10,000 per month from the sale of this product. Law enforcement officials seized 1,076 khat plants in September 1998.

The STRIDE reported drug items containing cathine and cathinone, the active constituents of Khat (see table below).

STRIDE Data for Cathine and Cathinone (2000 – 2005)

Drug	*2000*	*2001*	*2002*	*2003*	*2004*	*2005**	*Total*
Cathine	6	5	27	22	14	11	85
Cathinone	15	11	35	40	11	18	130

*Data through November 15, 2005

Similarly, the National Forensic Laboratory Information System (NFLIS), a Drug Enforcement Administration (DEA) sponsored project to systematically collect drug analyses results from state and local forensic laboratories, also reported drug items containing cathine and cathinone.

NFLIS Data for Cathine and Cathinone (2000 – 2005)

Drug	*2000*	*2001*	*2002*	*2003*	*2004*	*2005**	*Total*
Cathine	20	6	30	33	22	23	134
Cathinone	26	33	77	135	45	62	378

* Data through November 15, 2005

It is not clear from the NFLIS database whether khat is the source material for cathine and cathinone drug items analyzed. However, the law enforcement is not aware of illicit distribution of cathine and cathinone per se. The search of STRIDE database (federal seizures) of cathine and cathinone drug items revealed khat as the source material at least in seven (one in 2001 and six in 2002) instances. No such information is available for 2003 through 2005.

Khat Seizures (in grams) by the U.S. Law Enforcement (Source: El Paso Intelligence Center)

2000	*2001*	*2002*	*2003*	*2004*	*2005**
31,963,464	38,757,195	37,039,460	54,251,187	46,549,218	31,537,749

*Data through September 2005.

4. IMPACT OF SCHEDULING

4.1 If khat is placed under international control, do you think that its availability for medical use will be affected? No

Cathinone and cathine, the active constituents of khat, are controlled as Schedules I and IV of the Controlled Substances Act (CSA), respectively. In the United States, khat is subject to Schedule I controls when it contains cathinone. When it contains only cathine, it is subject to Schedule IV controls. International control of khat at similar level of regulatory control would not require a change in the level of control of this substance in the United States.

4.2 If "yes", how do you think the transfer will impact its medical availability? N/A

6. TRAMADOL (INN)

1. LEGITIMATE USE OF THE SUBSTANCE

1.1 Is the substance currently registered as a medical product? Yes (See attachment 5, package insert for Ultram)

If "yes", since when (year of marketing)?

Tramadol is a centrally acting analgesic that has been marketed in the United States since March 3, 1995 for the management of moderate to moderately-severe pain. A combination product containing 37.5 mg tramadol hydrochloride and 325 mg acetaminophen was approved for marketing in the United States on August 15, 2001. On May 5, 2005, the orally disintegrating tablet was approved and the extended release tablet products were approved on September 8, 2005. The table below provides detailed information about the products dosage forms, strengths and indications.

Tramadol Products Marketed in the U.S.

Trade name	*Dosage form*	*Strength(s)*	*Indication(s)*
Ultram	Tablet	50 mg	For the management of moderate to moderately severe pain in adults
Tramadol hydrochloride	Tablet	50 mg	For the management of moderate to moderately severe pain in adults
Tramadol hydrochloride	Orally disintegrating tablet	50 mg	For the management of moderate to moderately severe pain in adults
Ultracet	Tablet	325 mg; 37.5 mg	For the short term (five days or less) management of acute pain
Acetaminophen and tramadol hydrochloride	Tablet	325 mg; 37.5 mg	For the short term (five days or less) management of acute pain
Tramadol hydrochloride	Extended release tablet	100, 200 and 300 mg	For the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time

Currently, 13 pharmaceutical companies produce generic versions of the tramadol 50mg tablet formulation and two companies market generic versions of Ultracet. In 2004, there were approximately 19 million prescriptions dispensed for all tramadol products.

1.2 If the answer to 1.1 is "no", is there other legitimate use of the substance? N/A

1.3 If there is legitimate use of the substance, how is the substance supplied? (Imported / Manufactured in the country)

Tramadol is imported from the countries of Israel, Italy, Germany, Switzerland, and Ireland.

2. ABUSE OF THE SUBSTANCE

2.1 Is the substance abused or misused in your country? Yes

2.2 If "yes", any information on the extent of abuse?

Recent DAWN, NSDUH, and literature reports demonstrate abuse of tramadol since it was first marketed in the United States. Tramadol doses ranging from 100 mg to as high as 4 grams per day have been abused to achieve the opioid-like "high."

The HHS/FDA Adverse Events Reporting System, MedWatch, contains volunteer reports of adverse events associated with drugs. From its initial marketing in 1995 through September 2004, MedWatch received 766 case reports of abuse and 482 cases of withdrawal symptoms associated with tramadol.

The National Survey on Drug Use and Health (NSDUH) reported that the non-medical use of tramadol increased from 52,000 in 2002 to 186,000 in 2003. Around 1.3 million (0.5 percent) persons aged 12 or older have used tramadol products nonmedically in their lifetime. No data is available on current use. The NSDUH also reported that since 2004, approximately 1.3 million (0.5 percent) persons aged 12 or older have used tramadol products nonmedically in their lifetime.

The Drug Abuse Warning Network (DAWN) collects data on drug-related emergency department (ED) visits from a nationally representative sample of hospitals in the U.S. and a selection of metropolitan areas. Major changes were introduced to DAWN in 2003, including changes in the case definition, case types, data collection methodology and sample. Because of the many changes introduced in 2003, the most recent estimates available from DAWN are for the second half of the year (6 months) only and pertain to the coterminous U.S. only. Also because of the changes, comparisons cannot be made with any estimates prior to 2003.

DAWN reported that tramadol was involved in 1,119 drug misuse/abuse emergency department visits (95 percent CI 633 – 1,605) in the second half of 2003 in the United States.

Until 2002, the Drug Abuse Warning Network ("old" DAWN) on all drugs mentioned in drug abuse-related ED visits. Old DAWN reported that in 2002 alone, there were 1,714 ED visits that involved tramadol. From 1995 to 2002, mentions of tramadol in drug abuse-related ED visits increased 166 percent (Table 2).

Table 2. DAWN (Drug Abuse Warning Network) Estimate of Tramadol Mentions in Drug Abuse-Related ED Visits in the Coterminous US: 1995-2002* (Old DAWN)

Drug	*1995*	*1996*	*1997*	*1998*	*1999*	*2000*	*2001*	*2002*
Tramadol	645	1290	1418	1972	1113	1810	2329	1714

**Source: Substance Abuse and Mental Health Services Administration, Office of Applied Studies, Drug Abuse Warning Network.*

The Drug Abuse Warning Network also collects data on drug-related deaths that were investigated by participating medical examiners and coroners in major metropolitan areas across the U.S. The data do not represent the U.S. as a whole, nor do they necessarily represent the total number of deaths in which drug abuse was a causal or contributing factor. Rather, DAWN cases reflect the actual number (i.e., a census) of drug-related deaths reviewed, identified, and reported by the participating medical examiners and coroners (ME/Cs) in selected areas.

In old DAWN, participating medical examiners submitted data only for drug abuse-related deaths. DAWN Medical Examiner (ME) historical data for tramadol for the time period 1997 to 2002 is listed below in Table 3. Because the response rate can vary from year to year, DAWN uses a panel of medical examiners/coroners who submitted data consistently (a *consistent panel*) to identify trends. The consistent panel for 1997 to 2002 shows an increase in deaths involving tramadol in the participating areas (Table 3).

Table 3. Drug Abuse Warning Network (DAWN)[*]: Drug Abuse-Related Deaths Involving Tramadol from a Consistently Reporting Panel[1] of Medical Examiners: 1997-2002

Drug	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**
Tramadol	45	46	58	72	86	88

[*]Source: Substance Abuse and Mental Health Services Administration, Office of Applied Studies, Drug Abuse Warning Network

[1] Deaths reported by a consistent panel of medical examiners in 28 metropolitan areas. Consistent panels include only those jurisdictions that reported at least 10 months of data each year from 1997-2002. The panel does not include New York City (which did not submit data for 2001) or Los Angeles (which did not submit data for 2002).

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The American Association of Poison Control Centers (AAPCC) data suggest that tramadol products are involved in a number of toxic exposures that have resulted in at least 37 deaths from January 2003 through December 2004. Poison Control Center data for total exposures for tramadol single entity product (alone) and tramadol in combination with acetaminophen (APAP) are summarized in table 4 below.

Table 4. Poison Control Center Data for Tramadol

	2002		***2003***		***2004***	
	APAP	ALONE	APAP	ALONE	APAP	ALONE
Tramadol Exposures	862	3043	1330	3235	1542	3968

2.3 Any information on the extent of public health or social problems associated with the abuse of the substance (statistics on cases of overdose deaths, dependence, etc.)?

Tramadol is marketed in the United States without CSA controls that regulate the marketing and distribution of other μ-opioids. Tramadol abuse is reported and evidenced by data from a variety of sources. In a recently published study of impaired health care professionals (Knisely et al, 2002), a highly skilled group of individuals with access to the drug and who are knowledgeable about the drug's pharmacology, demonstrated a high abuse potential of tramadol.

The abuse potential of tramadol primarily results from the *m*-opioid activity of its active metabolite. Production of analgesia, euphoria, and "drug liking" are largely attributed to the active metabolite. In some individuals, the abuse potential of tramadol may be mitigated by several factors including the serotonin and norepinephrine reuptake properties of the parent drug, and pharmacokinetic features that include a delayed onset of *m*-opioid properties of the metabolite, or a genetic inability to metabolize the drug. Also, because of the duration of activity of the metabolite, the opioid withdrawal symptoms are expected to be less intense than other more strictly controlled opiates. The withdrawal symptoms of tramadol are sometimes reported to be typical of serotoninergic drugs. Tramadol overdose produces CNS depression, sedation, miosis, lethargy, respiratory depression and psychomotor agitation.

Tramadol differs from the class of μ-opioid agonists, in its greater tendency to cause excitatory effects, such as seizures. Excitatory effects, including seizures, may be exacerbated by other opioids, benzodiazepines, alcohol, barbiturates and gamma-hydroxybutyrate (GHB). Toxicity of tramadol appears due in part to its atypical monoamine reuptake inhibition as well as opioid effects.

For additional information, see attached product labels.

Drug sponsors provide postmarketing reports to HHS/FDA that originate from health care professionals and consumers. The reports have both strengths and weaknesses. They often provide valuable details about events that demonstrate that individuals may be taking the substance on their own initiative rather than on the basis of medical advice from a healthcare provider. These Adverse Drug Reaction Reports (ADEs) include descriptions of diversion, "doctor shopping" or manipulation of the dosage form to enhance the euphoric effects of the drug. However, those spontaneous reports are difficult to quantify. Also, the ADEs are useful for providing signals of problems that are detected relatively early in a drug's marketing cycle. With regard to the reports for tramadol in this document, the ADEs were collected over an 8-year period from the date of approval for marketing (March 3, 1995) to May 31, 2003. An assessment of the cause of the ADEs is not implied. Both patients with histories of drug or substance abuse and no prior history of substance abuse were reported.

Some signals detected from ADEs in postmarketing reports provided by the sponsor to the HHS/FDA include the following:

- Tramadol is obtained by diversion, including purchased "on the street" or by way of multiple prescriptions by individuals who abuse drugs.
- Opioid addicts take tramadol for euphoric effects produced primarily at higher doses, as well as to prevent the withdrawal symptoms from other opiates, and as a substitute

for other opiates when access is limited.

- Those individuals who abuse tramadol for its euphoric properties take large daily doses (600 to 3,500 mg) and therefore often experience toxicities and other aversive effects.
- Patients obtain tramadol prescriptions from multiple physicians and multiple pharmacies.
- Adolescents are reported to have crushed tablets of tramadol for intranasal administration.
- Some overdose deaths have involved use of tramadol in conjunction with alcohol or other drugs of abuse, such as cocaine.
- Many of the reports described drug abuse, dependence, or withdrawal occurring in health care professionals. The health care professionals include psychiatrists, surgeons, anesthesiologists, family physicians, medical residents, nurses, and pharmacy employees.
- Many of the reports describe individuals seeking euphoria, patients with opiate abuse histories, individuals who experiment with the drug, methadone clinic patients, and heroin addicts. In each of these cases, tramadol was self-administered for abuse.

From 1995 to 2002, tramadol was involved in an increasing number of drug abuse-related ED visits (from 645 in 1995 to 1,714 in 2002, an increase of 165 percent) (Table 2). As Table 3 illustrated, data from a consistent panel of medical examiners showed that in their jurisdictions, there was an increase in the number of drug abuse-related deaths that involved tramadol.

3. ILLICIT ACTIVITIES INVOLVING THE SUBSTANCE

3.1 Any information on the nature and extent of illicit activities involving the substance (clandestine manufacture, smuggling, diversion, seizure, etc.)?

Diverted pharmaceutical products are the only source for tramadol abuse. There is no data to suggest that this substance is clandestinely produced. The extent of diversion of this substance is difficult to estimate. Law enforcement encounters and forensic laboratory analysis are not good indicators of the extent of diversion and abuse of an uncontrolled pharmaceutical product. Despite this fact, tramadol has been seized by law enforcement and forensic laboratories have analyzed this substance as drug evidence. According to the NFLIS, and the STRIDE, increasing amounts of tramadol are being encountered by law enforcement personnel and analyzed in forensic laboratories (see table below).

NFLIS and STRIDE Data for Tramadol (1998 – 2005)

Source	*1998*	*1999*	*2000*	*2001*	*2002*	*2003*	*2004*	*2005**	*SUM*
NFLIS	12	47	79	146	244	267	303	381	1479
STRIDE	0	0	1	5	2	2	20	12	42
TOTAL	12	47	80	151	246	269	323	393	1521

* Data through November 15, 2005

In 2004, the total number of NFLIS and STRIDE exhibits for tramadol (303/20)

exceeds that of some controlled opioids including meperidine (231/27), fentanyl (198/13) and buprenorphine (148/5).

4. IMPACT OF SCHEDULING

4.1 If tramadol is placed under international control, do you think that its availability for medical use will be affected?

Currently, tramadol is a non-controlled opioid pharmaceutical in the United States. International control would require the United States to schedule this substance under the Controlled Substances Act (CSA). Appropriate international control should not have a significant impact on the legitimate medical use of tramadol in the U.S.

4.2 If "yes", how do you think the transfer will impact its medical availability? N/A

7. ZOPICLONE

1. LEGITIMATE USE OF THIS SUBSTANCE

1.1 Is the substance currently registered as a medical product? Yes (See attachment 6, package insert for Lunesta)

Zopiclone, is a mixture composed of equal amounts of two optical isomers identified as (*S*)-zopiclone or eszopiclone, and (*R*)-zopiclone. Eszopiclone is the most active component of the racemic (*R*,*S*) zopiclone, whereas the (*R*) isomer or (*R*)-zopiclone is the least potent component of the racemic mixture. In the United States only the (*S*) isomer (eszopiclone) is available for medical use.

If "Yes", since when (Year of marketing)?

Zopiclone has been controlled in Schedule IV of the Controlled Substances Act (CSA) since its marketing in April 2005.

Zopiclone Products

Trade name	*Dosage form*	*Strength(s)*	*Indication(s)*
Lunesta	Tablet	1, 2, and 3 mg	Lunesta is indicated for the treatment of insomnia (Label Attached)

1.2 If the answer 1.1 is "no", is there other legitimate use of the substance? N/A

1.3 If there is legitimate use of the substance, how is the substance supplied? (Imported/Manufactured in the country)

The drug substance, eszopiclone, is manufactured from the racemic mixture either in the United States or Canada. Racemic mixture, zopiclone, is manufactured in India.

2 ABUSE OF THE SUBSTANCE

2.1 Is the substance abused or misused[8] in your country?

Since zopiclone has only recently been approved for marketing in the United States, there is no evidence of significance abuse of either zopiclone or eszopiclone in the United States. From 1995 to 2004, only one seizure by DEA was reported in 2000 when four zopiclone tablets contained in a square fold blister package were seized in the U.S. State of Washington.

According to the FDA, eszopiclone has been recently introduced on the market, launching in December 2004 with marketing starting April 2005. Through October 2005,

[8] In this Questionnaire, "abuse or misuse" refers to the use of the substance other than for medical or scientific purposes.

2,088,000 prescriptions had been dispensed in the U.S.A. by retail pharmacies including chain, independent, food stores and mass merchandisers (Source: VECTOR ONE, Verispan, LLC)."

2.2 If "yes", any information on the extent of abuse? No

2.3 Any information on the extent of public health or social problems associated with the abuse of the substance (statistics on cases of overdose deaths, dependence, etc.)?

As a recently marketed drug (April 2005), DEA has received no reports of abuse of zopiclone or its isomers. Thus, there is no evidence of adverse public health or social problems reported in the U.S. as a consequence of abuse of zopiclone or its isomers. However, oral administration of eszopiclone, in Sepracor sponsored clinical trials, has been shown to elicit an adverse event profile comparable to that of other hypnotics. The observed adverse events included hallucinations, amnesia, difficulty concentrating, memory impairment, depression, somnolence, and accidental injury. Consistent with reports with zopiclone, patients consistently reported an unpleasant or bitter taste following the oral administration of eszopiclone.

In a clinical trial, there was one case of eszopiclone overdose. The subject was a 24-year old female who ingested 18 tablets from the study blister pack; total amount consumed was estimated to be between 18 and 36 mg. Approximately three hours after ingestion, the patient presented to the emergency room with her friend. She was described as drowsy, but responsive. She remained in the hospital overnight for observation. The patient fully recovered and was discharged in the morning with resolution of her symptoms, and without apparent sequelae.

There is also a reported case of a zopiclone overdose death in a 72 year old woman with respiratory debilitation due to bronchogenic carcinoma (Bramness et al., J. Forensic. Sci. 2001: 46, 1247-1249).

Eszopiclone is not marketed in other countries, but it is considered the active isomer of the racemic mixture zopiclone. Therefore, data on abuse and misuse of eszopiclone might be used when evaluating actual abuse and history of abuse of zopiclone.

In a study of abuse liability conducted in individuals with known histories of benzodiazepine abuse, eszopiclone at doses of 6 and 12 mg produced euphoric effects similar to those of diazepam 20 mg. In this study, at doses 2-fold or greater than the maximum recommended doses, a dose-related increase in reports of amnesia and hallucinations was observed for both Lunesta and diazepam.

Eszopiclone appears to pose the same risks to the public health as those exhibited by other benzodiazepines and other sedative hypnotics such as zolpidem, which are Schedule IV controlled substances under the CSA.

In clinical trials, eszopiclone showed an adverse event profile comparable to that of other hypnotics. Observed adverse events included hallucinations, amnesia, difficulty concentrating, memory impairment, depression, somnolence, and accidental injury.

The clinical trial experience with eszopiclone revealed no evidence of a serious withdrawal syndrome. Nevertheless, the following adverse events included in DSM-IV criteria for uncomplicated sedative/hypnotic withdrawal were reported during clinical trials following placebo substitution occurring within 48 hours following the last eszopiclone treatment: anxiety, abnormal dreams, nausea, and upset stomach. These reported adverse events occurred at an incidence of 2 percent or less.

Some loss of efficacy to the hypnotic effect of benzodiazepines and benzodiazepine-like agents may develop after repeated use of these drugs for a few weeks. Tolerance to the efficacy of eszopiclone 3 mg was assessed by 4-week objective and 6-week subjective measurements of time to sleep onset and sleep maintenance for eszopiclone in a placebo-controlled 44-day study, and by subjective assessments of time to sleep onset, and wake-time-after-sleep-onset (waso) in a placebo-controlled study for six months. Although no development of tolerance to any parameter of sleep measurement was observed over six months in clinical trials, it is known that some loss of efficacy to the hypnotic effect of benzodiazepines and benzodiazepine-like agents such as eszopiclone and zopiclone may develop after repeated use of these drugs for a few weeks.

3 ILLICIT ACTIVITIES INVOLVING THE SUBSTANCE

3.1 Any information on the nature and extent of illicit activities involving the substance (clandestine manufacture, smuggling, diversion, seizures, etc.)?

From 1995 to 2004, there was only one zopiclone seizure reported in 2000. Four zopiclone tablets contained in a square fold blister package were seized in the U.S. State of Washington. Because the zopiclone product was not marketed in United States in 2004, it is likely that the source of the drug is a country from other than the United States.

4 IMPACT OF SCHEDULING

If zopiclone is placed under international control, do you think that its availability for medical use will be affected? No

This substance is already controlled in Schedule IV of the U.S. Controlled Substances Act. International control would not require a change in the level of control of this substance in the United States.

4.1 If "yes", would the reduction adversely affect the provisions of medical care? N/A

1. **IMPACT OF TRANSFER TO SCHEDULE I OF THE SINGLE CONVENTION ON NARCOTIC DRUGS, 1961, ON MEDICAL AVAILABILITY**

1.1 If buprenorphine is transferred from Schedule III of the Convention on Psychotropic Substances, 1971, to Schedule I of the Single Convention on Narcotic drugs, 1961, do you think that its availability for medical use will be affected?

Buprenorphine substance and all products containing buprenorphine are currently controlled in Schedule III of the U.S. Controlled Substances Act (CSA). In 2002, two buprenorphine products were approved for narcotic addiction treatment in the United States. Prior to that time, buprenorphine was available as a Schedule V parenteral analgesic product.

If buprenorphine substance is transferred internationally from Schedule III of the Psychotropic Convention to Schedule I of the Single Convention on Narcotic Drugs, it is the view of the Department of Health and Human Services (DHHS) that the availability of buprenorphine products for medical use in the United States could be affected. In order to comply with the Single Convention and the CSA, buprenorphine substance would be transferred to Schedule II of the CSA. Rescheduling buprenorphine substance and products to Schedule II of the CSA to comply with international reclassification as a narcotic would thus prevent the use of buprenorphine products in the outpatient addiction treatment because of the unique regulation of narcotic addiction treatment in the United States, unless buprenorphine products are separately controlled in Schedule III of the CSA.

The U.S. Drug Enforcement Administration (DEA), which bears statutory authority to implement and enforce the CSA, provided the following comments: "Should buprenorphine be placed in Schedule I or II of the Single Convention, the U.S. would need to place bulk buprenorphine in Schedule II of the CSA. However, products of buprenorphine would not require Schedule II control. Schedule III controls under the CSA of buprenorphine products would be sufficient to meet the requirements of Schedule I or II controls under the Single Convention." It is DEA's view that this international scheduling action would not adversely affect the availability of buprenorphine products for medical use in the United States, especially in regard to the use of buprenorphine for narcotic treatment in accordance with the Drug Addiction Treatment Act (DATA, 21 U.S.C. 823).

The Drug Addiction Treatment Act (DATA) enacted in 2000 permits physicians to prescribe Schedule III to V narcotics, specifically approved for opiate addiction therapy, for use in office-based treatment. Prior to DATA, narcotic addiction treatment was restricted to specially licensed treatment facilities (so called methadone treatment centers) which limited access to medical treatment of opiate addiction. Following the enactment of DATA and the approval of the new buprenorphine products (Suboxone and Subutex, Schedule III) opiate addiction treatment was expanded.

Since Suboxone (buprenorphine combined with naloxone, package insert-attachment 7) and Subutex (single entity buprenorphine, package insert-attachment 7) became available in early 2003, over 6,500 physicians have sought and obtained the required DEA and SAMHSA authorization to use buprenorphine products for treatment of opiate addiction in office-based

settings. Approximately 70% of these physicians have prescribed the new products. (SAMHSA Buprenorphine Waiver System Database; January 17, 2006, available from SAMHSA/CSAT Division of Pharmacologic Therapy, 240-276-2716).

In 2005, an estimated 105,000 patients received buprenorphine for maintenance or detoxification treatment. Sixty percent of these patients were new to medication assisted treatment. (Results from SAMHSA/CSAT's Evaluation of the Buprenorphine Waiver Program, presented to the College on Problems of Drug Dependence, June 20, 2005)

An additional consideration is that individual States may regulate drugs more (but not less) restrictively than does the U.S. Federal Government. If States responded to the proposed international rescheduling of buprenorphine by controlling buprenorphine products more restrictively (State Schedule II), access to buprenorphine could be limited.

1.2 If "yes", how do you think the transfer will impact its medical availability?

See responses to 1.1

Comments from individuals, industry, and representatives for industry were submitted in response to the Federal Register Notice on the WHO Questionnaire. These comments are appended to the United States submission as attachments 8 through 14.

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