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Drug Enforcement Administration

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Food and Drug Administration
12420 Parklawn Drive
Room 1-23
Rockville, Maryland 20857

To Whom It May Concern:

The Drug Enforcement Administration (DEA) has completed and attached our review of the available data regarding the abuse of 4-bromo-2,5-dimethoxyphenethylamine (2-CB), gamma hydroxybutyric acid (GHB), 4-methylthioamphetamine (4-MTA), N-Methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB), diazepam, and zolpidem. These data could be incorporated into the critical reviews to be used for the 32nd World Health Organization (WHO) Expert Committee on Drug Dependence.

We are pleased to be providing such important data to WHO for its critical review and prereview documents.

Sincerely,

Frank Sapienza, Chief
Drug and Chemical Evaluation Section

Enclosures

00N-1257

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

COUNTRY NAME: United States

AGENCY NAME: Drug Enforcement Administration (DEA)

CONTACT PERSON: Frank Sapienza
Phone: (202) 307-7183; FAX: (202) 307-8570
E-mail address: fsapi@aol.com

1. 4-BROMO-2,5-DIMETHOXYPHENETHYLAMINE (2C-B)

1. LEGITIMATE USE OF 2C-B

- 1.1. 2C-B is not a medical product in the United States.
- 1.2. There is no legitimate use for this drug in the U.S.

2. ABUSE OF 2C-B

- 2.1. 2C-B is abused in the U.S.
- 2.2. 2C-B is promoted as a substance to enhance inter-communication and sexual pleasure. It has been encountered at raves and techno parties. However, the extent of 2C-B abuse is believed to be relatively small compared to other club drugs (seizures of MDMA are far in excess to that of 2C-B). It is generally abused orally at a dose of about 5 - 10 mg (10 mg tablets and capsules have been the most frequently encountered dose and form). It has been available as a powder for snorting and found on blotter paper and in sugar cubes.
- 2.3. The DEA is unaware of any overdose deaths. There have been no emergency room mentions in the Drug Abuse Warning Network (DAWN) in the past three years

3. ILLICIT ACTIVITIES INVOLVING 2C-B

- 3.1. 2C-B was first encountered on the illicit market in the U.S. in the 1970s. Until the early 1990s, very little abuse or trafficking in this substance was evident with only sporadic law enforcement encounters and small scale clandestine production. Clandestine laboratories were seized in California (1986 and 1994) and in Arizona (1992). Synthesis does not require extensive chemical knowledge or sophisticated equipment. Chemicals needed for synthesis are readily available from chemical supply companies.

In 1993, activities involving 2C-B changed considerably with a large distribution network that was trafficking thousands of dosage units of 2C-B under the brand name of Nexus. This 2C-B product was being manufactured in South Africa and illicitly smuggled into the U.S. in kilogram quantities. Nexus was distributed to at least 23 different states and 67 cities and known on the streets as Bromo, Spectrum and Nexus. Purchase price ranged from \$15 to \$30. The DEA placed 2C-B (including salts, isomers and salts of isomers: isomers include optical, positional and geometric) in Schedule I of the Controlled Substances Act (CSA) in June 1995.

Since January 1996, the DEA forensic laboratories have identified 2C-B in 17 exhibits involving 13 cases from 8 different states (DEA STRIDE Data).

These cases involved the seizure of 7,077 tablets, 3 capsules, 0.273 grams of powder and 30 milliliters of liquid. Recent seizures of 2C-B in Massachusetts and Mississippi have been reported in *Microgram* (November 1998, Volume 31, page 292; October 1999, Volume 32, p249).

2. GAMMA HYDROXYBUTYRIC ACID (GHB)

1. LEGITIMATE USE OF GHB

- 1.1** GHB is a Schedule I controlled substance and is not approved for marketing in the United States. Gamma hydroxybutyric acid, including its salts, optical isomers, and salts of optical isomers, became a Schedule I controlled substance on March 13, 2000.
- 1.2** There is no approved medical use for this drug in the United States. GHB is currently being studied by a pharmaceutical company for the treatment of cataplexy associated with narcolepsy.

2. ABUSE OF GHB

- 2.1** GHB is abused in the United States.

Since 1992, abuse, overdose, clandestine manufacture, and trafficking of GHB can be seen in nearly every U.S. state. GHB is easily synthesized in clandestine laboratories. This abuse has been facilitated by the proliferation of websites selling GHB kits and providing information on how to manufacture GHB at home.

- 2.2** **Extent of the Abuse with GHB**

DEA has documented over 9,600 adverse reactions, overdoses, and other cases from many drug abuse indicators and other sources since 1992. GHB is popular with a wide range of abusers in the US, including high school and college students, and rave party attendees who use the drug for purposes of intoxication. Body builders also abuse GHB for its purported anabolic effects. There are reports of use of GHB to incapacitate women for purposes of committing sexual assault.

In the late 1980's GHB began to be used as a steroid substitute and was used by bodybuilders and sold in health food stores and gymnasiums. In 1990, the FDA issued its first health warning about GHB declaring it a dangerous, unapproved drug after the CDC published a study of its toxicity and adverse events associated with its use. The FDA health alert on GHB was reissued in 1997 with additional deaths, overdoses and adverse events described by the CDC.

Since the early 1990's GHB has been sold in nightclubs, rave parties and bars. Kits and recipes for making GHB "home-brew" were available for sale over the Internet. GHB has been made in small quantities using these kits on college campuses and in larger scale clandestine laboratories using the two precursors, gamma butyrolactone (GBL) and sodium hydroxide (lye).

2.3 Public Health or Social Problems Associate with GHB Abuse.

Overdoses: Since 1993, over 9,600 encounters with GHB have been documented by information gathered from law enforcement, poison control centers and hospitals in 46 states. Of these, there are approximately 8,200 overdose cases attributed to GHB abuse reported from 1996-1998.

DAWN Emergency room episodes: From 1992-1998, the number of Drug Abuse Warning Network (DAWN) estimated emergency room episodes has risen steadily. The DAWN listed 20 emergency room episodes in 1992; since that time the number of episodes has steadily climbed: 1993 - 38; 1994 - 55; 1995 - 150; 1996 - 696, 1997 - 764, 1998 - 1343. Over 60% of the abusers were between the ages of 18 and 25 years. It was reported that the motivation for using GHB was for recreational abuse (61%), psychedelic effects (11%) and dependence (12%). The reason for the GHB emergency room visit was overdose (61%) and unexpected reaction (36%). GHB is abused exclusively by the oral route of administration and in 40% of the episodes, GHB was used alone. When used in combination, it is used most commonly with alcohol.

GHB-dependence: Recent studies and case reports show that chronic GHB use produces psychological and physical dependence and a withdrawal syndrome upon termination of use. The behaviors and associated problems in abusers of GHB are documented (Galloway et al. (1994, 1997; Dyer, 1999 and others) taken together with data from the DAWN system and from the numerous overdose cases reported by Poison Control Centers, law enforcement officers, and medical reports demonstrate that GHB produces drug dependence. These reports show that there is evidence of chronic self-administration, compulsive abuse despite adverse consequences, as well as drug seeking behavior. Both psychological and physical dependence may contribute to the continued abuse of GHB.

GHB-related deaths: Although no nationwide reporting system for drug related deaths exists, the DEA has collected investigative, toxicology and autopsy reports in which GHB was found in the biological fluids of the deceased. Since 1990, the DEA has identified 68 GHB related deaths, however the greatest numbers of deaths have occurred in the last four years. The majority of the deaths have occurred within the 20-29 year age group (58%). Additionally, 10% of the decedents were 14-19 years old and 21% were 30-39 years old. Sixty percent of the decedents were male and 93% were white. There were deaths reported from a total of 22 states and two foreign countries (Italy and England).

Use of GHB in sexual assault: Since 1996, DEA has received reports that substantiate the use of GHB to physically incapacitate women in order 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. The DEA is aware of at least eighteen sexual assault cases involving 43 victims of GHB in California, Colorado, Florida, Louisiana, Maine, Maryland, Massachusetts, Michigan, Texas, Utah, and Wisconsin. In the cases in Florida, Texas, Maryland and Wisconsin the GHB was detected in the urine of the sexual assault victims.

In response to a 1998 field survey on GHB, DEA received a total of 110 suspected, but not confirmed, GHB-facilitated sexual assaults complaints involving GHB and one case of involuntary ingestion followed by sexual assault. These reports came from rape crisis centers and hospitals. There were no toxicology results to verify whether GHB was used or how it was administered to the victim. Of these 110 cases, 40 were reported from a nurse practitioner in Salt Lake City, Utah, and 30 cases were reported from the Washington D.C. Rape Crisis Center. In these cases, the women reporting the sexual assault complaints all fit the profile of GHB-intoxication, but all the victims reported the incidents outside the time frame where GHB could be found in the urine. The other 40 complaints of sexual assault were received from agencies providing sexual assault services in twelve states.

Hoffman-LaRoche date rape drug testing program/EISohly report.

Between May 1996 and January 11, 2000, Hoffman-LaRoche supported a testing program to assay urine samples of suspected victims of drug-induced sexual assault. Over a 3½ year period, state and local law enforcement organizations, hospitals or rape crisis centers had the option to send urine samples from victims of alleged sexual assault to EISohly Laboratories in Mississippi. EISohly Laboratories conducted the urine testing and confirmed positive samples using gas chromatography/mass spectrum analytic methodologies. Of the 3143 samples tested, 1212 contained no drugs or alcohol. Of the remaining 1931 samples, some contained more than one substance, including alcohol. Of the 1931 samples, 90 were found to contain GHB. (EISohly and Salamone, 1999; Hoffman-LaRoche 2000).

3. ILLICIT ACTIVITIES INVOLVING GHB

At the time that much of these data were collected GHB was not a federally controlled substance; therefore it was not a target or priority of DEA law enforcement activity. For these reasons, the abuse and trafficking of GHB is severely underreported.

3.1 Law enforcement cases: Since 1993, DEA has documented approximately 1,400 law enforcement cases involving GHB, including clandestine laboratories, forensic analyses, possession, trafficking, and driving under the influence cases. In illicit traffic, GHB is most commonly found in liquid form in vials or small bottles, or sometimes as powdered material.

Driving under the influence and other law enforcement cases: Since 1993, DEA has documented 247 state or local law enforcement cases involving GHB, including driving under the influence (45 cases), overdoses (28 cases), GHB possession (51 cases), trafficking (30 cases), seizure (73 cases), undercover purchase of GHB (10 cases) and suspicious GBL orders (for clandestine GHB manufacture) (10 cases).

Clandestine manufacture: GHB has been produced exclusively in clandestine laboratories using a simple synthesis and available and inexpensive starting materials. The sodium salt of GHB is known as sodium oxybate and has a number of other chemical names. Gamma-butyrolactone (GBL) is an industrial solvent that can be purchased from chemical distributors and is used in the clandestine manufacture of GHB. GHB is produced in clandestine laboratories using a relatively simple synthesis with readily available and inexpensive starting materials. The illicit synthesis of yields GHB in solution as a clear liquid. GHB is encountered in a variety of containers, including water bottles, plastic bags, vials, gallon milk containers, buckets and 55-gallon drums. Confiscated samples have also been found in "spring water" bottles or disguised as mouthwash. DEA has received documentation of 175 GHB clandestine. These capacity of labs ranged from 389 grams to 60 gallons.

Forensic Analyses: GHB has been analyzed as evidence in law enforcement cases by forensic laboratories of the federal (DEA) and state and local agencies. All these data sources show an escalating number of cases since 1996. Data from DEA's STRIDE system revealed 154 exhibits of GHB were analyzed from 1994-April 2000. Of these, 76% were liquid samples accounting for 48,000 mls of GHB. Since 1993, DEA has received forensic analyses on a total of 556 exhibits of GHB. In these cases, GHB seizures ranged up to 60 gallons of liquid and up to 32 kg of powdered material.

3. 4-METHYLTHIOAMPHETAMINE (4-MTA)

1. LEGITIMATE USE OF 4-MTA

- 1.1** 4-MTA is not a medical product in the United States.
- 1.2** There is no legitimate use for this drug in the United States.

2. ABUSE OF 4-MTA

- 2.1** 4-MTA has not been identified as a drug of abuse in the United States.

3. ILLICIT ACTIVITIES INVOLVING 4-MTA

- 3.1.** 4-MTA has not been encountered by the DEA nor are we aware of any illicit production, distribution, or abuse in the U.S.

4. N-METHYL-1-(3,4-METHYLENEDIOXYPHENYL)-2-BUTANAMIDE (MBDB)

1. LEGITIMATE USE OF MBDB

- 1.1 MBDB is not marketed in the United States.
- 1.2 There is no legitimate use for this substance in the United States and is controlled in Schedule I of the Controlled Substances Act (CSA) as a positional isomer of 3,4-methylenedioxy -N-ethylamphetamine (MDE).

2. ABUSE OF MBDB

- 2.1 MBDB has been encountered on the illicit market in the U.S.
- 2.2 This drug is reported to produce effects similar to MDMA but at higher doses and is assumed to be used by the same individuals that would abuse MDMA. The extent of MBDB abuse is unknown but considered to be far less than MDMA.
- 2.2 The DEA is unaware of any deaths or emergency room visits in the U.S. associated with this drug.

3. ILLICIT ACTIVITIES INVOLVING MBDB

- 3.1 The DEA has not identified any clandestine manufacture of MBDB in the United States. However, logos on tablets of several forensic laboratory exhibits of seized MBDB are very similar to those seen in exhibits from other countries (Israel and Spain, *Microgram*).

Since 1995, MBDB has been encountered in at least 10 different states across the U.S. The seizures are generally quite small ranging from one or two tablets to about 200. The DEA forensic laboratories have analyzed 3 exhibits for a total of 6.5 tablets since 1995.

5. DIAZEPAM (INN)

2. LEGITIMATE USE OF DIAZEPAM

- 2.1 Diazepam is currently available for medical use in the United States.
- 2.2 Diazepam is a Schedule IV controlled substance that was approved for marketing in 1963.
- 2.3 Since 1994, the total number of prescriptions of diazepam has decreased every year. There were approximately 1 million fewer diazepam prescriptions in 1998 than in 1994.

2. ABUSE OF DIAZEPAM

- 2.1 Diazepam is abused, diverted and trafficked on the illicit market in the United States.
- 2.3 Abundant reports of actual abuse and diversion of diazepam can be defined by episodes/mentions in the databases indicative of abuse/dependence, and include data from the Drug Abuse Warning Network (DAWN), DEA's STRIDE system, state and local forensic laboratories, and United States Customs Service seizures/cases.
- 2.4 **DAWN Emergency room episodes:** From 1994-1998, the number of DAWN estimated emergency room episodes has remained relatively stable: 13,566 – 1994; 14,485 in 1995; 13,601 in 1996; 13,360 in 1997 and 12,758 in 1998. During this time, the number of total annual prescriptions for diazepam has decreased. When normalized with total annual diazepam prescriptions (IMS data), the numbers of estimated DAWN episodes are 114 per 100,000 prescriptions in 1997 and 105 per 100,000 in 1998.

The DAWN data shows that diazepam is taken orally (99%) in an attempt to commit suicide (60%), dependence (21%), for its other psychological effects (11%) or for recreational use (6%). The typical DAWN episode with diazepam involved a white (87%), female (56%)[male (44%)]. The DAWN episodes involved individuals of every age: most commonly within the age ranges of 30-39 years (35%), 40-49 years (22%), 20-29 years old (22%). These episodes most often involved an overdose (74%). The DAWN reports found diazepam used alone on 16% of occasions. When used in combination, diazepam was most often taken with alcohol (53%), cocaine (13%), marijuana (7%), opiates (26%), and other benzodiazepines (14%). Large numbers of hospital emergency episodes were reported in twenty-two US cities.

3. ILLICIT ACTIVITIES INVOLVING DIAZEPAM

There is a large amount of actual abuse and diversion of diazepam. This cursory review of several of the databases and descriptions of trafficking of diazepam represents only a small portion of these data gathered and analyzed.

3.1 DEA STRIDE Data: The DEA's System to Retrieve Information from Drug Evidence (STRIDE) was examined for diazepam mentions for the period January 1, 1994 through February 2000. There are over 1,350 separate exhibits for diazepam, indicating a substantial amount of illegal activity surrounding this drug. This pattern for diazepam has been evident from the 1970's.

During this 6-year period (1994-2000), there are more than 1,350 separate laboratory exhibits for diazepam, involved over 26 million tablets, 2,500 capsules, 105,000 grams of powdered material and 300 ml of liquid material. These exhibits were submitted for analysis in over 600 separate DEA and non-DEA cases in 41 states and the District of Columbia, Puerto Rico, and the U.S. Virgin Islands, Bahamas, Canada, Cameroon, India, Bangladesh, Guam, Pakistan. Over 90% of the cases in STRIDE involved seizures of tablets containing 10 or 5 mg of diazepam.

The majority of these cases (71%) involved the purchase or seizure of 100 or less tablets. However, there were 140 cases involving the purchase or seizure of thousands or tens of thousands of tablets each. There were 6 cases that involved the purchase or seizure of several hundred thousand tablets (range 103,000 to 400,000 tablets). In these 6 cases alone, a total of 1.4 million 10 mg tablets were seized; these seizures were made in California, Texas, Florida, and the Bahamas. Additionally, there were 3 cases that involved the seizure of hundreds of thousands or millions of low potency tablets (range 215,000 to 1,600,000 tablets, accounting for a total of 2.4 million tablets. These tablets were often found in packages labeled as "Miracle Herb" product, "Tung Shueh" or were labeled with Chinese writing.

State and Local Forensic Analyses: DEA has received a sampling of 1998 and 1999 data on the results of forensic analyses on a total of 2,361 exhibits of diazepam from state and local forensic laboratories. The majority of these exhibits were tablet form accounting for 74,000 grams of diazepam.

US Customs Service Data (USCS) The USCS data are derived from a seizure incidence report database known as Seized Asset and Case Tracking System (SEACATS). The drugs are seized by USCS as they were being smuggled into the United States at US points of entry. The seized drugs may or may not be subsequently analyzed in a testing laboratory.

DEA reviewed the 1997-1999 USCS seizure incident report data for 16 benzodiazepines currently approved for marketing in the United States. For

all three years, diazepam was the most frequently encountered benzodiazepine, accounting for 1,137 cases, 1,993 cases and 4,957 cases in 1997, 1998 and 1999, respectively. For comparison, the second most frequently encountered benzodiazepine was alprazolam, accounting for 225 cases, 589 cases and 2014 cases in 1997, 1998 and 1999, respectively.

4. IMPACT OF TRANSFER TO SCHEDULE III ON MEDICAL AVAILABILITY

- 4.1** There is **no** evidence that transfer of diazepam to Schedule III of the Convention on Psychotropic Substances, 1971 will affect its availability for medical use in the United States.
- 4.2** A transfer of diazepam to Schedule III will not affect medical availability in the United States.

6. ZOLPIDEM (INN)

1. LEGITIMATE USE OF ZOLPIDEM

- 1.1** Zolpidem is an FDA- approved drug marketed under the trade name Ambien. Zolpidem, its salts, isomers and salts of isomers, is a Schedule IV controlled substance in the United States.
- 1.2** Zolpidem has been available for marketing in the United States since 1993
- 1.3** Ambien (zolpidem tartrate) is available as 5 and 10 mg tablets for use in the short-term treatment of insomnia. Since 1993, the annual total number of prescriptions for Ambien (zolpidem) has increased 3-fold.

3. ABUSE OF ZOLPIDEM

- 3.1** Zolpidem is abused, diverted and trafficked in the United States.
- 3.2.** From 1994-1998, the DAWN system has documented a total of 21,860 estimated episodes. The number of estimated episodes increased in 1994 and 1995 and has remained relatively stable from 1996-1998: 1422 in 1994; 3918 in 1995, 5444 in 1996; 5453 in 1997 and 5623 in 1998. When normalized with total annual zolpidem prescriptions (IMS data), the numbers of estimated DAWN episodes are 62 per 100,000 prescriptions in 1997 and 56 per 100,000 in 1998.

Zolpidem is taken orally (99%) either in an attempt to commit suicide (75%) or for its other psychological effects (17%). The typical DAWN episode involved a white (88%), female (71%), within the age ranges of 35-45 years (30%), 25-34 years old (25%). These episodes most often involved an overdose (91%) or other unexpected response (3%). The DAWN reports found zolpidem used alone on 33% of occasions. When used in combination, zolpidem was most often taken with alcohol (44%), or other benzodiazepines (40%). Large numbers of hospital emergency episodes were reported in twenty-two US cities.

4. ILLICIT ACTIVITIES INVOLVING ZOLPIDEM

- 4.1.** From 1994-February 2000, the DEA forensic laboratory STRIDE system has encountered 46 exhibits of zolpidem totaling over 1,000 tablets (42 exhibits), 150 capsules (1 exhibit) and 63 grams of powdered material (3 exhibits). These cases occurred in nineteen different U.S. states.

Zolpidem has been used as a date-rape drug in the United States. DEA is aware of a recent case in Minnesota where a man was convicted of using zolpidem to incapacitate two women in order to commit sexual assault.

5. IMPACT OF SCHEDULING

- 5.1.** Zolpidem is currently a Schedule IV controlled substance in the United States. There is no indication that this control status has affected its availability for medical use in the United States. Since its marketing in 1994, total annual prescriptions for zolpidem have increased at a rate of approximately 1.5 million prescriptions every year to a total of nearly 12 million prescriptions in 1999.

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CONTACT PERSON: Frank Sapienza
Phone: (202) 307-7183; FAX: (202) 307-8570
E-mail address: fsapi@aol.com