National Institute of Allergy and Infectious Diseases, and John G. Bartlett, M.D. Professor of Medicine and Chief of Infectious Diseases at Johns Hopkins University School of Medicine. The 32-member panel includes Federal, private sector and academic experts in the clinical treatment and care HIV-infected people and representatives of AIDS interest groups, health policy groups and payer organizations.

Dated: June 16, 1997.

**John M. Eisenberg,**

*Principal Deputy Assistant Secretary for Health, U.S. Department of Health and Human Services.*

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

**[Docket No. 97N–0221]**

### Benzodiazepines and Related Substances; Criteria for Scheduling Recommendations Under the Controlled Substance Act; Notice of Public Hearing

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice of public hearing.

**SUMMARY:** The Food and Drug Administration (FDA) in conjunction with other Federal agencies will convene a part 15 public hearing on benzodiazepines and related substances. The purpose of the hearing is to gather evidence in order to assess the abuse potential of benzodiazepines and related compounds and to develop criteria that will distinguish the substances in order to address their appropriate scheduling under the Controlled Substance Act (the CSA).

**DATES:** The hearing will be held on Thursday and Friday, September 11 and 12, 1997, from 9 a.m. to 4 p.m. Written notice of participation should be filed by August 14, 1997. The closing date for comments will be October 17, 1997.

**ADDRESSES:** The public hearing will be held at the Renaissance Hotel, 999 Ninth St. NW., Washington, DC 20001–9000. Written notices of participation and any comments are to be sent to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Transcripts of the public hearing may be requested in writing from the Freedom of Information Office (HFI–35), Food and Drug Administration, 5600 Fishers Lane, rm. 12A–16, Rockville, MD 20857, approximately 15 working days after the hearing, at a cost of 10 cents per page. The transcript of the public hearing, copies of data and information submitted during the hearing, and any written comments will be available for review at the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

**FOR FURTHER INFORMATION CONTACT:** Nicholas P. Reuter, Office of Health Affairs (HFY–20), Food and Drug Administration, 5600 Fishers Lane, rm. 15–22, Rockville, MD 20857, 301–827–1696, FAX 301–443–0232, e-mail ''nreuter@bangate.fda.gov''.

**SUPPLEMENTARY INFORMATION:**

## I. Background

Benzodiazepines and related drug substances have consistently ranked among the most widely prescribed drug products in the United States. These products are used extensively as anxiolytics, sedatives, and hypnotics. Concomitant with the widespread use of these products have been concerns associated with benzodiazepine abuse, misuse, and the level of domestic and international control applied to these substances.

Benzodiazepines act upon the central nervous system (CNS). In addition, benzodiazepine substances have the potential for abuse and the capacity to produce physical and psychological dependence. As such, benzodiazepine substances have been subject to domestic and international drug control reviews. For the most part, until recently, these international and domestic reviews have resulted in uniform domestic and international controls. Essentially, all benzodiazepines and related compounds are controlled domestically in schedule IV of the CSA. In the most recent benzodiazepine-type substance domestic scheduling review, Ambien® (Zolpidem), was added to Schedule IV of the CSA in 1993. Internationally, most benzodiazepines are controlled in Schedule IV of the Convention on Psychotropic Substances, 1971 (the Convention). However, in 1990, the World Health Organization (WHO) reviewed, but did not recommend control of, three benzodiazepine substances (brotizolam, etizolam, and quazepam).

In response to a request from the Drug Enforcement Administration (DEA), the Department of Health and Human Services (DHHS) is currently evaluating the abuse liability of quazepam, a benzodiazepine controlled in Schedule IV of the CSA. The DEA request followed a petition from the company that manufactures a drug product containing quazepam as the active ingredient (Doral®). In its petition, the manufacturer requests that quazepam be removed from Schedule IV of the CSA and decontrolled.

### *A. International Reviews*

Benzodiazepines and related substances are psychotropics and are subject to the Convention. The domestic review and control of many benzodiazepine substances has been directly influenced by international scheduling actions. This is because the United States is expected to control substances domestically to fulfill international scheduling actions under the Convention. In addition, although the findings necessary for control under the Convention and the CSA are not identical, the schedule structure and issues surrounding the international and domestic control actions on benzodiazepines are similar and overlap. As discussed in section I.A.1., 2., and 3 of this document, the international scheduling review policy has evolved between the initial class reviews in the 1980's and the more recent substance oriented assessments.

#### 1. The 1984 Review

The United Nations (UN) Commission on Narcotic Drugs added 33 benzodiazepine substances to Schedule IV of the Convention (NAR/CL.4/1984; DND 421/12(1-7)) in March, 1984. The UN action followed an extensive review by the WHO, which had recommended that all 33 substances be controlled in Schedule IV. The WHO considered the following information in evaluating the need for international control:

(1) Chemical structure, receptor binding characteristics, sedative-hypnotic, anticonvulsant, and anxiolytic profile of CNS effects;

(2) Animal data on psychological and physical dependence potential;

(3) Human experimental data on both dependence and abuse potential;

(4) Clinical data on dependence and public health problems;

(5) Epidemiological data on public health and social problems;

(6) Extent of abuse or likelihood of abuse and seriousness of public health and social problems resulting from such abuse; and

(7) Utilization and usefulness in therapy.

The WHO found that for many of the 33 benzodiazepine substances, no data were available other than for items (1) and (4) listed previously. In recommending international control, however, the WHO determined that if a

drug under review possessed characteristics fulfilling item (1) listed previously, the drug had the capacity to produce a state of dependence and the likelihood of abuse constituted a public health and social problem warranting international control (48 FR 53754, November 29, 1983; see also 48 FR 23913, May 27, 1983).

After reviewing written comments and convening a public meeting on the WHO recommendations, DHHS concluded that there was sufficient evidence, in the form of significant actual abuse or trafficking data or compelling preclinical and clinical abuse liability data on 18 of the 33 substances that the WHO was recommending for control. DHHS was not aware of similar data for the remaining 15 benzodiazepine substances that the WHO was recommending for international control. In essence, the United States disagreed with the WHO assessment that the chemical and pharmacological similarity of all 33 benzodiazepine substances were sufficient to warrant international scheduling.

2. The 1991 Review

The WHO reconsidered the international control of benzodiazepine substances again in 1989. In 1989, a WHO expert committee (the Expert Committee on Drug Dependence (ECDD)) reviewed four benzodiazepine substances, midazolam, brotizolam, etizolam, and quazepam. The ECDD recommended that only one of these substances, midazolam, be added to Schedule IV of the CSA. According to the 26th ECDD report, midazolam's control was based on the water solubility of midazolam's salts, and evidence of actual abuse associated with midazolam (Ref. 1). In 1990, the U.N. subsequently voted to add midazolam to Schedule IV of the Convention.

In 1990, the ECDD examined the issue of differential scheduling among the 34 benzodiazepine substances controlled in Schedule IV of the Convention (33 initial substances plus midazolam). The United States forwarded abuse liability, trafficking, and other pertinent data to the WHO as part of this review (see 54 FR 38441, September 18, 1989, and 54 FR 42844, October 18, 1989). The ECDD considered extensive prereview documents (Ref. 2) on each substance and again determined that three benzodiazepine substances that were not controlled (brotizolam, etizolam, and quazepam) should not be controlled because the ''degree of seriousness of the public health and social problems associated with the abuse of [these substances] was not great enough to warrant international control (Ref. 3).''

The ECDD also considered the information available on the 34 benzodiazepine substances that were already controlled internationally. The ECDD differentiated the 34 substances into the following 3 categories:

(1) Nineteen benzodiazepine substances were found to be appropriately controlled at their present level (Schedule IV of the Convention). The ECDD determined that they needed no further action. The nineteen substances are:

TABLE 1—NINETEEN BENZODIAZEPINE SUBSTANCES CONSIDERED APPROPRIATELY CONTROLLED BY THE ECDD

| Substances | | |
|---|---|---|
| Alprazolam | Halazopam | Nitrazepam |
| Bromazepam | Ketazolam | Oxazepam |
| Chlordiazepoxide | Lorazepam | Prazepam |
| Clobazam | Lometazepam | Temazepam |
| Clonazepam | Medazepam | Triazolam |
| Chlorazepate | Midazolam | |
| Flurazepam | Nimetazepam | |

(2) The ECDD found that the 13 substances below have high to moderate therapeutic usefulness, with few or no reports of abuse or illicit activity. The ECDD recommended that the WHO monitor the substances to determine whether or not they should be considered for descheduling:

TABLE 2 —THIRTEEN BENZODIAZEPINE SUBSTANCES BEING CONSIDERED FOR RESCHEDULING BY THE ECDD

| Substances | | |
|---|---|---|
| Camazepam | Ethyl loflazepate | Nordiazepam |
| Clotazepam | Fludiazepam | Oxazolam |
| Cloxazolam | Haloxazolam | Pinazepam |
| Delorazepam | Loprazolam | Tetrazepam |
| Estazolam | | |

(3) Finally, the ECDD recommended that two substances, diazepam and flunitrazepam, should be monitored for appropriate scheduling. The ECDD found that:

* * *in comparison with all other benzodiazepines reviewed, diazepam and flunitrazepam showed a continuing higher incidence of abuse and association with illicit activities. The higher abuse potential of diazepam than that of several other benzodiazepine anxiolytics has also been demonstrated in human experimental studies and survey studies of drug abusers, supported by information received from health professionals engaged in the treatment of drug dependence.

The ECDD's differentiation of the controlled benzodiazepines and the recommendation for not controlling three substances were based on an evaluation of information in the following areas:

a. *Human pharmacokinetic studies*:

Onset of action, elimination time, and duration of effect after both single and repeated administrations may be important determinants of the dependence potential of individual substances. Active metabolites may contribute to the overall effects of a substance.

b. *Preclinical studies*:

(1) Drug discrimination.

(2) Physical dependence.

(3) Self-administration.

c. *Clinical studies*:

(1) Categorization of subjective effects in persons with histories of drug abuse.

(2) Determination of euphoriant, liking, and reinforcing effects in persons with histories of drug abuse.

(3) Assessment of physical dependence.

d. *Epidemiological data and information on illicit activities*:

(1) Utilization data.

(2) Reports of extent and nature of actual abuse.

(3)Survey data.

(4) Drug seizures.

(5) Reports of clandestine manufacture.

(6) Diversion from illicit sources.

e. *Clinical usefulness and breadth of therapeutic indications*:

In sum, the international review, culminating in 1991, strongly suggests that criteria can be developed and applied to differentiate the abuse liability of individual benzodiazepine substances. Importantly, the ECDD suggested that these criteria should be used collectively and that no one criterion could or should be used as a sole determinate for control.

3. The 1995 Review

In 1994 and 1995, the ECDD considered five benzodiazepine substances or benzodiazepine-related substances for possible changes in their control status under the Convention.

a. *Brotizolam*. The ECDD recommended that brotizolam should be added to Schedule IV of the Convention. This recommendation was based on studies that demonstrate that brotizolam is a short-acting hypnotic with a mean elimination half life of 4 to 5 hours. The ECDD also found that brotizolam produces mild-to-severe withdrawal symptoms that indicate that the substance has a moderate dependence potential similar to other benzodiazepine hypnotics. Brotizolam was found to have an appreciable abuse liability based on the actual abuse problems in two countries.

b. *Flunitrazepam*. The ECDD differentiated flunitrazepam from other benzodiazepines, including diazepam, and recommended that it be up-scheduled from Schedule IV to Schedule III of the Convention. The ECDD based its recommendation on flunitrazepam's effects on the central nervous system, on flunitrazepam's dependence potential, and on its actual abuse.

The ECDD found that flunitrazepam's pharmacology and central nervous system effects were different than other benzodiazepines:

Flunitrazepam has typical benzodiazepine effects, with a greater sedative-hypnotic potency than diazepam or chlordiazepoxide. Flunitrazepam binds with high affinity to central benzodiazepine receptors and is rapidly absorbed after oral administration. The elimination half-life of flunitrazepam following a single oral dose ranges between 9 and 25 hours in humans. Accumulation occurs with chronic administration (Ref. 4).

Further, the ECDD was able to distinguish flunitrazepam from other benzodiazepine substances on the basis of its dependence producing characteristics:

Drug preference studies in opioid users, however, have shown that flunitrazepam and diazepam stand out from other benzodiazepines by producing a strong positive reinforcing effect in these subjects. Flunitrazepam is estimated to have a moderate abuse potential which may be higher than that of other benzodiazepines. The rapid onset and longer duration of action, coupled with the stronger sedative-hypnotic effects, may contribute to its higher abuse potential (Ref. 5).

Finally, the ECDD found that flunitrazepam was reported to be the most [widely] abused benzodiazepine by opioid abusers in Europe, Asia, and Oceania. The health problems associated with the abuse of flunitrazepam ''include deaths directly or indirectly related to its use, drug dependence, withdrawal syndrome, paranoia, amnesia, and other psychiatric disorders.'' Although information available indicated that both diazepam and flunitrazepam were associated with a higher incidence of ''illicit activities'' when the ECDD factored in the amounts manufactured and potency, flunitrazepam could be distinguished with respect to both seizures of the drug and the number of cases.

c. *Zolpidem*. The ECDD noted that Zolpidem is a ligand that binds specifically to the $\omega_1$ benzodiazepine receptor. The committee characterized Zolpidem as a short-acting hypnotic that does not alter significantly natural sleep characteristics. The ECDD characterized zolpidem's abuse liability as minimal, which may be attributable to its short marketing history. The ECDD did not recommend further review of this substance.

d. *Zopiclone*. The ECDD noted that zopiclone is a hypnotic pharmacologically similar to benzodiazepines, binding to central, but not peripheral benzodiazepine, receptors. The ECDD rated zopiclone's dependence potential as comparable to benzodiazepines; however, its abuse liability could not be considered significant because there were so few reports of abuse despite availability in 40 countries. The ECDD did not recommend further review for control.

e. *Triazolam*. The ECDD determined that no scheduling recommendation was required for triazolam, but they suggested continued monitoring of abuse-related adverse reactions.

**B. Domestic Control Actions**

There are 36 benzodiazepine substances controlled domestically in Schedule IV the CSA. For the most part, these substances have been added to Schedule IV in groups.

(1) Six benzodiazepine substances were controlled in 1975 (40 FR 23998, June 4, 1975). These substances are: Chlordiazepoxide, clonazepam, clorazepate, diazepam, flurazepam, and oxazepam.

(2) An additional six benzodiazepine substances were controlled in Schedule IV between 1976 and 1984. These substances are: Prazepam (41 FR 55176, December 17, 1976), lorazepam (42 FR 54546, October 7, 1977), temazepam (46 FR 20671, April 7, 1981), halazepam (46 FR 53407, October 29, 1981), alprazolam (46 FR 55688, November 12, 1981), and triazolam (47 FR 57694, December 28, 1982).

The twelve substances listed under section II.B.(1) and (2) of this document had been approved for marketing by FDA prior to their control under the CSA, and prior to the international review that led to the initial international control of 33 benzodiazepine substances in 1984. These substances were the subject of scientific and medical reviews and scheduling recommendations by DHHS, as required under 21 U.S.C. 811(a)) of the CSA.

For the most part, the reviews and findings were similar, and did not reflect the application of criteria that would differentiate the individual substances.

(3) Twenty-one benzodiazepine substances were controlled ''temporarily'' in Schedule IV of the CSA in 1984 (49 FR 39307, October 5, 1984). These substances were not reviewed under the scheduling provisions of 21 U.S.C. 811(a) of the CSA. Instead, the substances were controlled domestically in schedule IV under the temporary control provisions of section 201(d) (4) of the CSA. DEA noted that the temporary scheduling order for each substance shall remain in effect until the process of permanent scheduling is completed under 21 U.S.C. 811(a) and (b) of the CSA (Ref. 6) None of the substances are marketed in the United States at this time. The 21 substances are:

TABLE 3—TWENTY-ONE BENZODIAZIPINE SUBSTANCES CONTROLLED UNDER SECTION 201(D)(4) OF THE CSA

| Substances | | |
|---|---|---|
| Bromazepam | Ethyl loflazepate | Nimetazepam |
| Camazepam | Fludiazepam | Nitrazepam |
| Clobazam | Flunitrazepam | Ordiazepam |
| Clotazepam | Haloxazolam | Oxazolam |
| Cloxazolam | Ketazolam | Pinazepam |
| Delorazepam | Loprazolam | Tetrazepam |
| Estazolam | Lormetazepam | Medazepam |

There was no attempt to examine the abuse liability of these substances individually. Indeed, in recommending the Schedule IV control to DEA, the Assistant Secretary for Health stated that ''[p]lacement of the following drug substances in Schedule IV would also control them similarly to other benzodiazepines already marketed in this country'' (Ref. 7).

(4) Two substances, midazolam and quazepam, were added to Schedule IV in 1986 (51 FR 10190, March 25, 1986). As discussed in section I.A.2 of this document, midazolam was controlled internationally in 1991.

(5) Zolpidem is the most recent benzodiazepine related substance to be controlled domestically. This substance was added to Schedule IV in 1993, following its review and approval by FDA and following a comprehensive medical and scientific evaluation by DHHS (58 FR 7186, February 5, 1993).

Zolpidem is a novel nonbenzodiazepine related hypnotic, that possesses an imidazopyridine structure. Although Zolpidem is chemically not a benzodiazepine and appears to have some distinct receptor binding activity at one identified benzodiazepine receptor, its pharmacology, psychological, and physical dependence liability do not appear overall to be any less than the other benzodiazepines that are currently listed in Schedule IV of the CSA.

In recommending Schedule IV control for zolpidem DHHS found that:

Zolpidem's potential for abuse is equal to or greater than triazolam's and the other benzodiazepines which are in Schedule IV. Zolpidem elicits many of the same pharmacological responses of the benzodiazepines. Its short duration of action and rapid onset enhance the likelihood that zolpidem would be a drug of abuse. In addition, zolpidem's water solubility, which is not a feature of most of the other marketed benzodiazepines, offers potentially an additional factor that could lead to greater abuse, by way of diversion and extraction of the drug substance for injection * * *. There are actual reports of abuse and dependence. The psychological and physical dependence capacity can be inferred from preclinical data and clinical pharmacology studies which describe tolerance development, drug discrimination properties, self-administration experiments, and adverse reaction reports from other countries.

(6) Flunitrazepam was added to Schedule IV of the CSA in 1984, along with 20 other benzodiazepine substances that had been reviewed and controlled as a class. In 1995, the U.N. moved flunitrazepam from Schedule IV to Schedule III of the Convention on Psychotropic Substances. The U. S. Government supported this action.

Flunitrazepam is the active ingredient in Rohypnol, that has been the subject of escalating abuse and trafficking in the United States in recent months. DEA initiated a review on flunitrazepam to determine if stricter controls are warranted to deter abuse and trafficking of this substance.

In response to a request from the Administrator of DEA, DHHS evaluated the abuse liability of flunitrazepam in accordance with the eight factors determinate of control under the CSA. In January 1997, DHHS concluded that the preclinical and clinical abuse liability research findings and the actual abuse of flunitrazepam do not significantly distinguish it from other benzodiazepines currently determined by DHHS to have a low abuse liability and controlled in Schedule IV. Furthermore, the same science suggests that the abuse liability of flunitrazepam is significantly less than that of the Schedule II barbiturates. Thus, DHHS advised DEA that the abuse potential of this drug, based on the factors applied by DHHS, is consistent with control under Schedule IV. In light of these findings, DHHS recommended that there be no change in the current scheduling of flunitrazepam under Schedule IV of the CSA.

(7) DHHS is currently evaluating the abuse liability of quazepam, a benzodiazepine controlled in Schedule IV of the CSA. Quazepam is the active ingredient in Doral®, which was approved for marketing in the United States in December 1985 and has been commercially available in the United States since March 1990. Quazepam was added to Schedule IV of the CSA in March 1986. In May 1992, the manufacturer of Doral® submitted a petition requesting that quazepam be removed from Schedule IV of the CSA and decontrolled.

The petitioner contends that quazepam should be decontrolled because the substance has no significant potential for abuse and does not lead to limited physical or psychological dependence. According to the petitioner, quazepam's abuse and dependence characteristics are influenced by its unique combination of pharmacologic and pharmacogenetic properties. Quazepam is relatively selective to the $BZ_1$ ($\omega$-1) receptor (as is zolpidem, previously). And, quazepam is highly lipophilic with long acting metabolites that may further reduce rebound insomnia and the risk of dependence. The petitioner argues that some studies suggest that quazepam, in contrast to other benzodiazepines, only partially suppresses the intermediate to severe withdrawal signs produced after barbital administration (Ref. 8).

## III. Discussion

Notwithstanding the exceptions noted in section I.A. 3 of this document, most currently controlled benzodiazepine substances were reviewed and controlled between 1983 and 1993 without differentiation. However, recent studies have suggested that benzodiazepine substances may be distinguishable by pharmacologic properties that influence their abuse liability characteristics.

A review of the clinical literature shows that benzodiazepines and other sedative/hypnotics may be differentiated with respect to their abuse liability and ''attractiveness'' to abusers. For example, a series of placebo-controlled, double-blind studies that compared the reinforcing/subjective effects of different benzodiazepines across a range of doses in sedative abusers found that there were meaningful differences among these compounds (Ref. 9). Specifically, lorazepam and diazepam appear to have high abuse liability, while oxazepam,

halazepam, and chlordiazepoxide have less potential for abuse than diazepam (Refs. 10 and 11). Diazepam has one of the most rapid onsets of action of all marketed benzodiazepines; in contrast, halazepam and oxazepam are among the slowest to produce effects. Thus, it has been suggested that the differentiation among benzodiazepines may be based on their pharmacokinetic profiles (fast versus slow onset of behavioral or subjective effects) (Refs. 9 and 12).

In addition, there is some evidence in the scientific literature that the results of self-administration studies in animals may differ for different benzodiazepines. These studies have often been used to compare the potential for psychological dependence on drug substances. Further, some benzodiazepine substances have been reported to produce marked, severe withdrawal syndromes in animals (including seizures). Other benzodiazepines have been reported to produce relatively mild withdrawal syndromes.

In sum, recent research suggests that benzodiazepines may be distinguishable on the basis of their specific potential for abuse. It is not clear, however, how valid these distinctions are and how reliably benzodiazepines can be differentiated on this basis. Further, there are also questions regarding how these characteristics should influence the type of restrictions and controls that may be applied to these substances. It is possible that, based on pharmacologic and abuse liability characteristics, some benzodiazepine substances warrant a higher level of control. For others, these characteristics could support a lesser level of control or perhaps decontrol. The purpose of this hearing will be to generate evidence with which to relate a substance's abuse characteristics with the legal criteria determinative for control.

*A. Criteria for and Procedures for Scheduling Reviews*

Under the CSA, the Secretary of DHHS is charged with evaluating medical and scientific factors and recommending to DEA whether the substance under review should be controlled or removed as a controlled substance and the appropriate level of control (if control is necessary). Under an interagency memorandum of understanding (Ref. 13), FDA and the National Institute on Drug Abuse (NIDA) participate in the medical review, evaluation, and recommendations that DHHS conducts as part of the domestic drug scheduling process.

The CSA establishes the factors and findings determinative for the control of substances in the United States. The factors set forth under 21 U.S.C. 811(a), (b), and (c) of the CSA are:

(1) Its actual or relative potential for abuse.

(2) Scientific evidence of its pharmacological effect, if known.

(3) The state of current scientific knowledge regarding the drug or other substance.

(4) Its history or current pattern of abuse.

(5) The scope, duration, and significance of abuse.

(6) What, if any, risk there is to the public health.

(7) Its psychic or physiological dependence liability.

(8) Whether the substance is an immediate precursor of a substance already controlled under this title.

To be controlled in any of the five schedules established by the CSA, the substance must meet certain findings relative to its potential for abuse as well as the physical and psychological dependence associated with such abuse (21 U.S.C. 811(c)). Currently, all benzodiazepine substances are controlled domestically in Schedule IV. The findings necessary for control in Schedule IV are:

(1) The drug or other substance has a low potential for abuse relative to other drugs or substances in Schedule III.

(2) The drug or other substance has a currently accepted medical use in treatment in the United States.

(3) The drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III.

*B. Need for Meaningful Criteria*

There are currently 36 benzodiazepine and related substances controlled in Schedule IV of the CSA. Of these, 15 are approved and marketed for medical use in the United States. A cursory review of the substances on this list suggests that there may be differences in their pharmacology. There may also be differences in the onset and duration of action. In addition, substances may differ in their abuse liability characteristics, including the ability to develop tolerance and produce dependence. These differences may be reflected in epidemiological data relating to abuse, as well as the illicit use and trafficking of the substances.

It is important that a substance's abuse potential and dependence producing characteristics are reflected in the substance's control under the CSA. This permits drug abuse control resources to be focused appropriately.

The criteria will be useful in identifying the types of information and scientific evidence needed to assess or differentiate the abuse potential for benzodiazepine and related compounds. These criteria will provide guidance to the industry about the types of studies to pursue and submit to address the abuse potential section of a new drug application. Moreover, the guidance developed will aid in evaluating the type of control necessary for such substances. As such, FDA and NIDA anticipate that the criteria and guidance will stimulate the development of drug products with lower abuse potential.

FDA and NIDA are inviting the pharmaceutical industry, academia, regulatory entities, law enforcement entities, consumer, and other entities to participate in this hearing.

**IV. Public Hearing Topics**

In order to promote a more useful discussion at the public hearing, FDA and NIDA developed a list of questions and issues. This list is not intended to be exclusive, and presentations and comments on other issues related to the criteria for controlling benzodiazepines and related substances are encouraged. The list follows:

(1) Is it possible to distinguish benzodiazepine and related substances on the basis of their abuse potential and dependence producing effects? If so, would such distinctions be useful in determining what level of control is appropriate under the CSA for a given benzodiazepine or related substance?

(2) Different types of data and information are traditionally used in making decisions on scheduling of substances under the CSA that can be grouped into four broad classes:

(a) Preclinical studies of abuse-related phenomena;

(b) Clinical studies of abuse-related phenomena (physiological dependence, subjective effects, psychological dependence, acute toxicity, tolerance, etc.);

(c) Epidemiologic studies of use and abuse of drugs; and

(d) Information gathered from various law enforcement agencies.

Within each of these broad classes there exists an array of types of pharmacological procedures and tests that are used to collect information relevant to abuse liability assessments.

(i) Are there preclinical test paradigms that can be meaningful and useful in distinguishing the abuse liability of benzodiazepine and related substances?

(ii) Are there clinical abuse liability studies that can be useful for assessing and distinguishing the abuse potential of benzodiazepines?

(iii) Are there pharmacodynamic characteristics (intrinsic efficacy, binding of subtypes of benzodiazepine receptors) and pharmacokinetic properties (e.g., its onset and duration of action, its active metabolites, etc.) that reliably distinguish among benzodiazepine and related substances with regard to their abuse or potential for abuse? If so, how does a benzodiazepine or related substances pharmacodynamic and pharmacokinetic properties influence its abuse or potential for abuse?

(iv) Are there reliable methods for using epidemiological, actual abuse, and trafficking data to distinguish among benzodiazepines for scheduling purposes? How should intentional overdose and suicide data be considered in this analysis?

(v) Are there other sources of information that can be used in assessing and distinguishing the abuse potential of benzodiazepine substances?

(vi) Are there test methods and procedures that have better predictive validity than others in assessing and distinguishing the abuse potential of benzodiazepines?

(3) What information should be included in the drug abuse/dependence portion of the benzodiazepine product labeling? Are there instances where a label warning could obviate the need for scheduling? Should the product's labeled indication (e.g., chronic insomnia, depression, anxiety, epilepsy, adjunct to anesthesia, etc.) influence the abuse potential and dependence potential assessment?

## V. Scope of Hearing

The purpose of this hearing is to generate evidence and information that will aid in developing criteria to evaluate the abuse liability characteristics of benzodiazepines. It is not the purpose of this hearing to evaluate and make recommendations on the control of specific substances, including substances that are the subject of current scheduling petitions.

## VI. Notice of Hearing Under 21 CFR Part 15

As discussed in sections III., IV., and V of this document, FDA believes the format and procedures of a public hearing, at which interested persons can testify, will best elicit the information needed to develop meaningful criteria for determining the appropriate level of control under the CSA for benzodiazepine and related substances. Accordingly, the Commissioner of Food and Drugs, is announcing a public hearing under part 15 (21 CFR part 15).

The public hearing is scheduled to begin at 9 a.m. at the Renaissance Hotel (address above), on September 11 and 12, 1997. The presiding officer, Stuart L. Nightingale, Associate Commissioner for Health Affairs, Food and Drug Administration, will be accompanied by a panel from FDA, the National Institutes of Health, DEA, and other DHHS employees with relevant expertise. The procedures governing the hearing are found at part 15.

Persons who wish to participate are requested to file a notice of participation with the Dockets Management Branch (address above) on or before August 14, 1997. To ensure timely handling, the outer envelope should be clearly marked with Docket No. 97N–0221 and the phrase ''Benzodiazepine Scheduling Criteria Hearing.'' The notice of participation should contain the interested person's name, address, telephone number, any business or organizational affiliation of the person desiring to make a presentation, a brief summary of the presentation, and the approximate time requested for the presentation. FDA may ask that groups having similar interests consolidate their comments as part of a panel. FDA will allocate the time available for the hearing among the persons who properly file notices of participation. If time permits, FDA may allow interested persons attending the hearing who did not submit a notice of participation in advance to make an oral presentation at the conclusion of the hearing.

Persons who find that there is insufficient time to submit the required information in writing may give oral notice of participation by calling Nicholas Reuter (telephone number above) no later than August 29, 1997. Those persons who give oral notice of participation should also submit written notice containing the information described above to the Dockets Management Branch by the close of business September 7, 1997.

After reviewing the notices of participation and accompanying information, FDA will schedule each appearance and notify each participant by mail or telephone of the time allotted to the persons and the approximate time the person's oral presentation is scheduled to begin. The hearing schedule will be available at the hearing, and after the hearing it will be placed on file in the Dockets Management Branch.

To provide time for all interested persons to submit data, information, or views on this subject, the administrative record of the hearing will remain open until October 17, 1997. Persons who wish to provide additional materials for consideration are to file these materials with the Dockets Management Branch (address above). To ensure timely handling, the outer envelope should be clearly marked with Docket No. 97N–0221 and the phrase ''Benzodiazepine Scheduling Criteria Hearing.''

The hearing is informal, and the rules of evidence do not apply. No participant may interrupt the presentation of another participant. Only the presiding officers and panel members may question any person during or at the conclusion of a presentation.

Public hearings, including hearings under part 15, are subject to FDA's guideline (21 CFR part 10, subpart C) concerning the policy and procedures for electronic media coverage of FDA's public administrative proceedings. Under 21 CFR 10.205, representatives of the electronic media may be permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public administrative proceedings, including presentations by participants.

To the extent that the conditions for the hearing, as described in this notice, conflict with any provisions set out in part 15, this notice acts as a suspension, modification, or waiver of those provisions as specified in 21 CFR 15.30(h).

## VII. References

The following information has been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. World Health Organization, Expert Committee for Drug Dependence, 26th Report.

2. World Health Organization, Pre-Review Data Sheets.

3. World Health Organization, Expert Committee for Drug Dependence, 27th Report.

4. World Health Organization, Expert Committee for Drug Dependence, 29th Report.

5. World Health Organization, Expert Committee for Drug Dependence, 29th Report.

6. Proposed Rule, **Federal Register** of August 1, 1984, 49 FR 30748.

7. Letter from Assistant Secretary for Health to Administrator, Drug Enforcement Administration, dated May 1, 1984.

8. Yanagita, T., ''Dependence Potential of the Benzodiazepines: Use of Animal Models for Assessment,'' *Clinical Neuropharmacology*, 8 (S1):S118–s–122, 1985.

9. Griffiths, R. R. and B. Wolf, ''Relative Abuse Liability of Difference

Benzodiazepines in Drug Abusers,'' *Journal of Clinical Psychopharmacology*, 10:237–243, 1990.

10. Griffiths, R. R. and J. D. Roache, ''Abuse Liability of Benzodiazepines: A Review of Human Studies Evaluation Subjective and/or Reinforcing Effects,'' In: *The Benzodiazepines: Current Standards for Medical Practice*, edited by D. E. Smith and D. R. Wesson, MTP Press Limited: Lancaster, England, pp. 1535-1541, 1985.

11. Funderburk, F. R. et al., ''Relative Abuse Liability of Lorazepam and Diazapam: An Evaluation in Recreational Drug Users,'' *Drug and Alcohol Dependence*, 22:215–222, 1988.

12. Juergens, S. M., ''Benzodiazepines and Addiction,'' *Recent Advances in Addictive Disorders*, 16:75–86, 1993.

13. Memorandum of Understanding With the National Institute on Drug Abuse, and the FDA, dated March 3, 1985 (50 FR 9518).

Dated: June 12, 1997.

**William K. Hubbard,**

*Associate Commissioner for Policy Coordination.*

[FR Doc. 97–16064 Filed 6–16–97; 2:51 pm]

**BILLING CODE 4160–01–F**

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

### Assuring Radiation Protection; Availability of Cooperative Agreement; Request for Applications

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA), Center for Devices and Radiological Health (CDRH), Office of Health and Industry Programs (OHIP), is announcing the availability of up to $1,500,000 in total costs (including both direct and indirect costs) per year, for a period of 5 years, for the establishment of a cooperative agreement to support efforts to coordinate Federal and State actions to assure radiation protection of the American public. Federal funds are currently available for this program, but an award is subject to the condition that funds are transferred to FDA from other Federal agencies to support this program.

**DATES:** Applications must be received by close of business on July 25, 1997.

**ADDRESSES:** Application kits are available from, and completed applications should be submitted to: Robert L. Robins, Grants Management Officer, Division of Contracts and Procurement Management (HFA–520), Food and Drug Administration, Park Bldg., 5600 Fishers Lane, rm. 3–40, Rockville, MD 20857, 301–443–6170.

**NOTE**: Applications hand-carried or commercially delivered should be addressed to Park Bldg., 12420 Parklawn Dr., rm. 3–40, Rockville, MD 20857. Please do NOT send applications to the Division of Research Grants, National Institutes of Health (NIH).

**FOR FURTHER INFORMATION CONTACT:**

Regarding the administrative and financial management aspects of this notice: Robert L. Robins (address above).

Regarding the programmatic aspects of this notice: Richard E. Gross, Center for Devices and Radiological Health (HFZ–200), Food and Drug Administration, 1350 Piccard Dr., Rockville, MD 20850, 301–443–2845.

**SUPPLEMENTARY INFORMATION:** FDA will support the efforts covered by this notice under section 532 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360ii). FDA's research program is described in the Catalog of Federal Domestic Assistance, No. 93.103.

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of ''Healthy People 2000,'' a PHS-led national activity for setting priority areas. This request for application (RFA), Assuring Radiation Protection, is related to the priority area of ''Healthy People 2000'' Cancer Objectives (chapter 16). Potential applicants may obtain a copy of ''Healthy People 2000'' (Full Report, Stock No. 017–001–00474–0) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402–9325, 202–512–1800.

PHS strongly encourages all grant recipients to provide a smoke-free workplace and to discourage the use of all tobacco products. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

#### I. Background

Since 1968, FDA, the Nuclear Regulatory Commission and its predecessor organizations, the Environmental Protection Agency and more recently, the Federal Emergency Management Agency and the Department of Energy have provided financial support for a forum for the exchange of ideas and information among the States and the Federal Government and to study existing and potential problems of radiation control. Other Federal agencies, notably the National Institute of Standards and Technology and the Centers for Disease Control and Prevention, have provided additional support for specific activities associated with the exchange of ideas and approaches for improving radiation control techniques. This forum has made it possible for State and Federal agencies to work together to study radiological health problems of mutual interest and to apply their increasingly limited resources with maximum effectiveness in seeking ways to control these public health problems.

Three major mechanisms have been used to achieve this coordination:

(1) When certain radiation control subjects warrant specific consideration, committees and other working groups composed of representatives of State radiation control programs and liaison members from the concerned Federal agencies have been formed to evaluate and offer solutions to the problems. The recommendations of the committees are evaluated by a central management board and final recommended actions are relayed to the appropriate Federal and State agencies.

(2) Annual meetings of Federal and State officials are convened to present and discuss the results of the studies conducted. The annual meetings also include workshops to more carefully define new problems and areas of mutual concern in radiation control, and clinics to demonstrate mutually beneficial radiological health techniques, procedures, and systems.

(3) Additional educational activities have been provided to members of State programs having radiation control responsibilities and to the general public to acquaint them with radiation exposure problems and the proposed solutions.

Methods used have included videotapes, publications, and training courses.

#### II. Goals and Objectives

The objective of this cooperative agreement will be to continue the Federal and State coordination activities with the goal of achieving effective solutions to present and future radiation control problems. The recipient of this cooperative agreement award will be expected to continue the annual meetings and to obtain the cooperation of the individual States in maintaining the system of committees and working groups established to deal with individual problems. Additionally, the recipient of this cooperative agreement award will be expected to continue to provide the leadership to refresh and update previously developed consensus