UNITED STATES DEPARTMENT OF JUSTICE

DRUG ENFORCEMENT ADMINISTRATION

In the Matter of	)	
	)	Docket No. 84-48
MDMA SCHEDULING	)	
	)	

AGENCY'S PROPOSED FINDINGS OF FACT, CONCLUSIONS OF LAW AND ARGUMENT

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Pursuant to the November 12, 1985 order of the Administrative Law Judge, the Department of Justice, Drug Enforcement Administration, by and through its undersigned attorneys hereby submits its proposed findings of fact, conclusions of law and argument.

INTRODUCTION

This proceeding is a rulemaking conducted pursuant to 21 U.S.C. §§ 811 and 812. The process was initiated by the Drug Enforcement Administration on July 27, 1984, when a Notice of Proposed Rulemaking was published in the Federal Register. 49 Fed. Reg. 30210 (July 27, 1984). (ALJ-1) 1/ The Drug Enforcement Administration proposed the placement of the substance, 3,4-methylenedioxymethamphetamine (MDMA) into Schedule I of the Controlled Substances Act, 21 U.S.C. § 801 et seq.

Sixteen comments and seven requests for hearing were received in response to the Notice of Proposed Rulemaking. Following prehearing procedures, there remained five parties, including the agency, participating in the hearing process. Five hearing sessions were held beginning on February 1, 1985 in Washington, D.C. and culminating on November 1, 1985, in Washington, D.C. The other hearing sessions were held on June 10, 1985 in Los Angeles, California, July 10 and 11 in Kansas City, Missouri, and October 8, 9, 10, 11, 1985 in Washington, D.C. The testimony of thirty-three

1/ ALJ- indicates Administrative Law Judge Exhibits, A- indicates an agency exhibit, GG-indicates an exhibit introduced by Drs. Greer and Grinspoon, et al.

witnesses was entered into the record. Ninety-five exhibits were introduced into evidence.

ISSUES

The following issues were provided by the Administrative Law Judge in a Memorandum to the Parties dated March 29, 1985. The Administrative Law Judge indicated that these issues, "should include all of the additional ones stated by the parties." 2/

1. Assuming that a substance has a potential for abuse and has no currently accepted medical use in treatment in the United States, can the substance be placed in any schedule other that Schedule I? 3/

2. What constitutes "currently accepted medical use in treatment in the United States" within the purview of 21 U.S.C. § 812(b)?

3. What constitutes "accepted safety for use . . . under medical supervision" within the purview of 21 U.S.C. § 812(b)?

4. Is a finding by the Secretary of Health and Human Services that a substance has "no currently accepted medical use in treatment in the United States" or a finding that a substance has no "accepted safety for use . . . under medical supervision" binding on the Attorney General (the Administrator of the Drug Enforcement

2/ In its prehearing statement dated March 11, 1985, the agency proposed the following issue, "What is the potential for abuse of MDMA relative to substances currently controlled under the Controlled Substances Act?" The agency considers this issue to be a crucial one in this proceeding and will address it as related to issue number 7.

3/ This issue was previously briefed by all parties and will not be addressed in this brief.

Administration, DEA) within the purview of the provisions of 21 U.S.C. § 812?

5. Does MDMA have a "currently accepted medical use in treatment in the United States" within the purview of 21 U.S.C. § 812(b)?

6. Is there a lack of "accepted safety for use [of MDMA] under medical supervision" within the purview of 21 U.S.C. § 812(b)?

7. If, on the basis of the resolution of the above issues, MDMA can lawfully be scheduled in a schedule other than Schedule I, in which schedule should it be placed?

SUMMARY OF THE AGENCY'S POSITION ON ISSUES

The Drug Enforcement Administration proposed the placement of 3,4-methylenedioxymethamphetamine (MDMA) in Schedule I and continues to maintain that Schedule I is the only schedule into which this substance can be placed. The agency's position on each of the previously stated issues in this case is as follows:

1. A substance which has a potential for abuse and no currently accepted medical use in treatment in the United States can only be placed in Schedule I pursuant to the provisions provided in 21 U.S.C. §§ 811 and 812.

2. The phrase "currently accepted medical use in treatment in the United States" as used in 21 U.S.C. § 812(b) means that the drug or other substance being considered for scheduling can be lawfully marketed in the United States under the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301 et seq.

3. The phrase "accepted safety for use under medical supervision" as used in 21 U.S.C. § 812(b) means that the drug or other substance has qualified to be lawfully marketed under the Federal Food, Drug and Cosmetic Act, and has been found by the Food and Drug Administration to be "safe" for marketing after a reveiw of the results of extensive preclinical and clinical testing.

4. All scientific and medical findings, including whether a substance has "no currently accepted medical use in treatment in the United States" and whether a substance has "accepted safety for use . . . under medical supervision," made by the Secretary of the Department of Health and Human Services are binding upon the Attorney General (the Administrator of the Drug Enforcement Administration, DEA).

5. MDMA does not have a "currently accepted medical use in treatment in the United States" since it may not be lawfully marketed in the United States under the provisions of the Federal Food, Drug and Cosmetic Act.

6. There is a lack of "accepted safety for use [of MDMA] under medical supervision" since it has not qualified for marketing under the Federal Food, Drug and Cosmetic Act and therefore has not been found "safe" for use.

7. 3,4-methylenedioxymethamphetamine (MDMA) has a high potential for abuse, therefore, if it cannot be placed in Schedule I pursuant to 21 U.S.C. §§ 811 and 812, it should be placed into Schedule II.

PROCEDURAL FACTS

1. On March 13, 1984, the then Administrator of the Drug Enforcement Administration Francis M. Mullen, Jr. sent a letter to Dr. Edward Brandt, Assistant Secretary of Health, Department of Health and Human Services requesting a scientific and medical evaluation and scheduling recommendation for the substance 3,4-methylenedioxymeth-amphetamine (MDMA). (A-B1) Enclosed with this letter was a document entitled, "Schedule I Control Recommendation Under the CSA for 3,4-Methylenedioxymethamphetamine (MDMA)." (GG-59)

2. On June 6, 1984, James F. Dickson, Acting Assistant Secretary for Health, Department of Health and Human Services sent a letter to Francis M. Mullen, Jr., Administrator of the Drug Enforcement Administration recommending that MDMA be placed in Schedule I of the Controlled Substances Act. (A-B3) Attached to this letter was the Department of Health and Human Services' evaluation of the DEA recommendation to control 3,4-methylenedioxymethamphetamine in Schedule I. (A-B4)

3. On July 27, 1984, the Drug Enforcement Administration published a Notice of Proposed Rulemaking in the Federal Register, 49 Fed. Reg. 30210, proposing the placement of 3,4-methylenedioxymeth-amphetamine (MDMA) into Schedule I of the Controlled Substances Act. (ALJ-1)

4. In response to the Notice of Proposed Rulemaking, the agency received sixteen comments and seven requests for a hearing. The matter was then referred to Administrative Law Judge Francis L. Young by the then Deputy Administrator of the Drug Enforcement Administration. (ALJ-2)

5. On December 31, 1984, a Notice of Hearing was published in the Federal Register, 49 Fed. Reg. 50732. The Notice invited any person who desired to participate in the hearing to file a written notice of intent to participate with the Administrative Law Judge. A preliminary hearing session was scheduled for February 1, 1985. (ALJ-2)

6. Following pre-hearing procedures, there remained five parties to the hearing including the agency. In addition to the agency, the parties are 1) Thomas B. Roberts, Ph.D., George Greer, M.D., James Bakalar and Lester Grinspoon, M.D.; 2) Hoffman LaRoche, Inc. and McNeilab, Inc.; 3) Lyn B. Ehrnstein; and 4) David E. Joranson. (ALJ-5)

7. The Administrative Law Judge required direct testimony to be submitted in writing and under oath. Identification of witnesses and direct testimony was required to be filed on April 25, 1985. (ALJ-5)

8. Cross-examination of witnesses was conducted in four hearing sessions. On June 10, 1985, witnesses were cross-examined in Los Angeles, California. On July 10 and 11, 1985, witnesses were cross-examined in Kansas City, Missouri. On October 8, 9, 10, 11 and November 1, 1985 witnesses were cross-examined in Washington, D.C. (ALJ-7, 8, Tr-4, pg. 193) 4/

4/ The transcripts of the various hearing sessions will be cited as follows:

February 1, 1985	Tr-1	October 9, 1985	Tr-6
June 10, 1985	Tr-2	October 10, 1985	Tr-7
July 10, 1985	Tr-3	October 11, 1985	Tr-8
July 11, 1985	Tr-4	November 1, 1985	Tr-9
October 8, 1985	Tr-5		

SCHEDULING CRITERIA

The Comprehensive Drug Abuse Prevention and Control Act of 1970 (Pub. L. 91-513), of which the Controlled Substances Act was Title II, was signed into law on October 27, 1970. Prior to that time abusable drugs and other substances were "controlled" by various provisions of the Internal Revenue Code of 1954, and the Drug Abuse Control Amendments to the Food, Drug and Cosmetic Act.

Sections 201 and 202 of the Controlled Substances Act (21 U.S.C. §§ 811 and 812) provide the authority for the Attorney General to control drugs or other substances and provide the criteria which are to be used to determine into which schedule a drug or other substance will be placed. 5/ These sections also outline the procedure to be used in the scheduling process. While proceedings to schedule a substance may be initiated by any interested party, the Attorney General is required to "gather the necessary data" and request a scientific and medical evaluation of the drug or other substance from the Secretary of the Department of Health and Human Services prior to initiating control proceedings. 6/ The legislative history of the Controlled Substances Act describes the "gathering of necessary data" as enabling the Attorney General to:

> defer submission of a request to the Secretary until the Attorney General, on the basis of all the information available to him - particularly any information developed by him as to the scope, pattern, and significance of abuse of a drug or substance in this country - has reason to

5/ The authority to control was subsequently delegated by the Attorney General to the Administrator of the Drug Enforcement Administration pursuant to 28 C.F.R. § 0.100(b).

6/ 21 U.S.C. § 811(a)

believe that there may be grounds for controlling or decontrolling a drug or other substance. 7/

Once the Attorney General (Administrator) has reason to believe that a drug or other substance should be controlled, a request for a scientific and medical evaluation and recommendation will be made to the Secretary of the Department of Health and Human Services. After the Secretary's written evaluation and recommendation are received by the Administrator, it will be considered along with all other information collected, and the Administrator will make a determination as to whether there is sufficient evidence of a potential for abuse to justify the initiation of control proceedings. The recommendations of the Secretary, however, are binding on the Administrator as to scientific and medical matters. 8/

The legislative history of the scheduling provisions of the Controlled Substances Act places great weight on the potential for abuse of the drug or other substance being considered for control under the Act. The House Report (H. Rep. No. 91-1444, 91st Cong., 2nd Sess.) explains that the term "potential for abuse" came from the Drug Abuse Control Amendments (DACA) of 1965, and was further characterized in regulations to that Act which were found at 21 C.F.R. § 166.2(e). There was also discussion of this term in House Report No. 130, 89th Cong., 1st. Sess. which accompanied the Drug Abuse Control Amendments of 1965. The House Report for the DACA 1965 stated with reqard to the term "potential" that:

> it did not intend that potential for abuse be determined on the basis of "isolated or occasional nontherapeutic purposes." The committee felt that there must exist "a substantial potential for the occurrence of significant

7/ [1970] U.S. Code Cong. & Admin. News 4600

8/ 21 U.S.C. § 811(b)

diversion from legitimate channels, significant use by individuals contrary to professional advice, or substantial capability of creating hazards to the health of the user or safety of the community." 9/

The regulations promulgated under DACA 1965, formerly found at 21 C.F.R § 166.2(e), defining potential for abuse stated:

> The Director may determine that a substance has a potential for abuse because of its depressant or stimulant effect on the central nervous system or its hallucinogenic effect if:
>
> (1) There is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or of the community; or
>
> (2) There is significant diversion of the drug or drugs containing such a substance from legitimate drug channels; or
>
> (3) Individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice; or
>
> (4) The drug or drugs containing such substance are new drugs so related in their action to a drug or drugs already listed as having a potential for abuse to make it likely that the drug will have the same potentiality for abuse as such drugs, thus making it reasonable to assume that there may be a significant diversion from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or the safety of the community. 10/

Utilizing this background to define what Congress intended by the term "potential for abuse" as used in the Controlled Substances Act, the Attorney General (Administrator) must determine, after all data is gathered and he has received the evaluation and recommendation of the Secretary, if there is substantial evidence of potential for abuse.

9/ [1970] U.S. Code Cong. & Admin. News 4602

10/ Id. 4601

The legislative history also indicates that, "Final control by the Attorney General will also be based on his findings as to the substance's potential for abuse." 11/ Thus, the term "potential for abuse" of a drug or other substance being considered for control is a threshold issue to be determined by the Administrator prior to intitiating scheduling proceedings, as well as a matter to be addressed in making findings regarding the schedule into which the drug or other substance will be placed.

Unless a drug or other substance is being controlled in order to fulfill international treaty obligations or because it is the immediate precursor of a substance already under control, the Administrator must make the following findings in order to place a drug or other substance into Schedule I:

(A) The drug or other substance has a high potential for abuse.

(B) The drug or other substance has no currently accepted medical use in treatment in the United States.

(C) There is a lack of accepted safety for use of the drug or other substance under medical supervision. 12/

In making these findings the Administrator shall consider the eight factors listed in 21 U.S.C. § 811(c). These same factors are to be utilized by the Secretary of the Department of Health and Human Services when providing a scientific and medical evaluation and recommendation as to scheduling pursuant to 21 U.S.C. § 811(b). The eight factors or areas to be reviewed in making the findings required

11/ Id. 4602

12/ 21 U.S.C. § 812(b)

by 21 U.S.C. § 812(b) for the drug or other substance in question 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 and 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 subchapter.

The factors listed above are considered by the Administrator in making his findings concerning accepted medical use, accepted safety for use, potential for abuse, and physical or psychological dependence. The Secretary of the Department of Health and Human Services is directed by the statute (21 U.S.C. § 811(b)) specifically to consider the factors regarding pharmacological effects of a substance (factor 2), state of current scientific knowledge (factor 3), risk to the public health (factor 6), psychic or physiological dependence liability of the substance (factor 7), and whether the substance is an immediate precursor of a substance already controlled (factor 8); in making the evaluation and recommendation required. The Secretary may also consider the scientific and medical elements of the other factors.

Once the Administrator has made the required findings, the proposal for scheduling under the Act is published in the Federal

Register as a Notice of Proposed Rulemaking. The rulemaking proceeding is then conducted "on the record after opportunity for a hearing" 13/ in accordance with the applicable procedures of the Administrative Procedure Act.

CURRENTLY ACCEPTED MEDICAL USE

There are two issues in this matter which deal with the concept of "currently accepted medical use." Issue number two addresses the meaning of the phrase as used in Section 812 of Title 21 United States Code, and issue number five addresses whether the substance MDMA has a "currently accepted medical use in treatment in the United States." Both of these issues will be addressed by the findings of fact and discussion in this section.

Findings of Fact

1. The National Conference of Commissioners on Uniform State Laws approved a Model Uniform Controlled Substances Act for adoption by the states in 1970. (Joranson, direct, p. 8)

2. The scheduling factors and criteria found in the Uniform Controlled Substances Act are nearly identical to those in the federal act. The Uniform Controlled Substances Act uses the phrase "accepted medical use in treatment in the United States" rather than the phrase "currently accepted medical use in treatment in the United States" used in the federal Controlled Substances Act. (Joranson, direct, p. 8, 9)

13/ 21 U.S.C. § 811(a)

3. In the commentary to the Uniform Controlled Substances Act there is the following statement:

> Based upon these criteria, hallucinogenic substances and certain narcotic substances are included in the same schedule. . . This is primarily because both groups of drugs have no accepted medical use in the United States and both have a high potential for abuse.
>
> Experimental substances found to have a potential for abuse in early testing will also be included in Schedule I. When those substances are accepted by the Federal Food and Drug Administration as being effective, they will then be considered to have an accepted medical use for treatment in the United States, and thus, will be eligible to be shifted to an appropriate schedule based upon the criteria set out in Sections 205, 207, 209, and 211. [Emphasis added]

(Joranson, direct, p. 9)

4. On March 21, 1984, the Controlled Substances Board of the State of Wisconsin unanimously adopted the following language in issuing a position on the meaning of the phrase, "accepted medical use in treatment in the United States":

> "currently accepted medical use in treatment in the United States" of a drug means that it is lawfully marketed in this country under the Federal Food, Drug and Cosmetic Act and that FDA's approval of a New Drug Application establishes this acceptance.

(Joranson, direct, p. 11)

5. The controlled substances scheduling authorities from the various states were surveyed via questionnaire prepared by Mr. David Joranson of the Wisconsin Controlled Substances Board. The questionnaire consisted of two questions. The first question was, "Does your state controlled substances law provide that only the substances in Schedule I have no accepted medical use in treatment in the U.S. and that the substances in Schedules II-V have accepted

medical use?" The second question was, "Is it your belief that the meaning of 'accepted medical use in treatment in the U.S.' under your law is consistent with the interpretation of the National Conference of Commissioners on Uniform State Laws, and the position of the Controlled Substances Board, as quoted in the attached letter to you?" A total of 43 states responded to the survey. The results were as follows:

Question 1	Yes	35
	No	4
	N/A	4
Question 2	Yes	39
	No	1
	N/A	4

(Joranson, amended direct, p. 3, 4, 5)

6. A new drug application (NDA) must be approved by the Food and Drug Administration prior to marketing a new drug in the United States. The NDA generally consists of data collected during the investigational new drug (IND) process. The data in the NDA must include toxicity studies, carcinogenic studies in animals, reproductive studies in animals, side effects in humans, and sufficient results from controlled studies to show that the drug is safe and effective in humans for the therapeutic purpose advanced by the sponsor. New drug applications have been required prior to marketing since 1938. (Tocus, direct, p. 3, 4)

7. Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) outlines the new drug application process. The statute

provides at Section 505(a) that, "No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) of this section is effective with respect to such drug." The statute further provides that a person filing an application for a new drug must include, "full reports of investigations which have been made to show whether such drug is effective in use." (Section 505(b)) (Tocus, direct, p. 4, Exhibit 2)

8. Section 505(i) of the Federal Food, Drug and Cosmetic Act allows the Secretary of the Department of Health and Human Services to exempt from the application of the requirements of approval of an NDA prior to marketing "drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs." The section goes further to delineate certain requirements which must be met by these experts. (Tocus, direct, Exhibit 2)

9. Before an unmarketed new drug may be tested on humans, an investigational new drug application (IND) must be submitted to and approved by the Food and Drug Administration. This approval is required for both pharmaceutical companies who ultimately intend to market the drug and physicians or researchers who are interested in using the drug solely as a research tool. These IND requirements are necessary to comply with provisions of the Federal Food, Drug and Cosmetic Act, its implementing regulations, and the basic ethical principles regarding the conduct of research in human subjects. These standards were established as a result of the Nuremberg trials

in the Nuremberg Code, and later reiterated in the Helsinki Agreement of 1975. 14/ (Tr-7, p. 103, 104; Tr-9, p. 64; GG-6)

10. In order for an IND to be initially approved by the Food and Drug Administration, the sponsor must provide information regarding the composition, source and manufacturing safeguards of the substance; animal toxicity studies showing that the substance will not produce irreversible damage at the doses used, and that there will be no unreasonable hazard in initiating studies in humans; a detailed research protocol of the proposed clinical investigation, information regarding the training and experiences of the investigators; and an agreement to notify the FDA if any adverse effects arise during animal or humans tests. (GG-6; Tocus, direct, p. 2, 3; Tr-9, p. 72, 73)

11. On June 29, 1982, the Food and Drug Administration (FDA) published in the Federal Register "Proposed Recommendations to the Drug Enforcement Administration Regarding the Scheduling Status of Marihuana and its Components and Notice of Public Hearing" (47 Fed. Reg. 28141) in which the Commissioner of Food and Drugs stated:

> FDA interprets the term "accepted medical use" to mean lawfully marketed under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301, et seq. . . . A drug may be marketed lawfully under the Federal Food, Drug, and Cosmetic Act after approval of a new drug application (NDA) for that drug. There are, theoretically other ways in which a drug could be marketed legally. The drug could satisfy either the requirements for exemption from the definition of "new drug" in 21 U.S.C. 321(p) or the requirements for a "grandfather clause" from the new drug approval provision. (47 Fed. Reg. 28150)

14/ For reference purposes, the Declaration of Helsinki is codified in the Code of Federal Regulations at 21 C.F.R. § 312.20, and is attached as Appendix 1.

The Commissioner of FDA continued at page 28151 by saying:

> The mechanism set up by Congress for lawful marketing of a new drug requires submission of an NDA to FDA and FDA approval of that application before marketing. Before FDA can approve an NDA, however, the drug sponsor must submit data from an extensive battery of experimental testing on both animals and humans to establish the drug's safety and effectiveness for its proposed uses. In addition, the sponsor must submit data and manufacturing controls demonstrating that standards of identity, strength, quality, and purity will be met.

and concludes by saying:

> Thus, the lack of an approved NDA for a drug substance leads FDA to find that a substance lacks an "accepted medical use in treatment" for two reasons. First, if use of the drug is unlawful whenever interstate commerce is involved, medical use of the drug cannot be classified as accepted. Second, in the absence of the data necessary for approval of an NDA, the agency has no basis for concluding that medical use of the drug in treatment can be considered acceptable by medical standards.

(A-B14)

12. In March, 1984, there was no reference in the files of the Food and Drug Administration to the substance 3,4-methylenedioxymeth-amphetamine (MDMA); there were no investigational new drug applications or approvals; there were no new drug applications or approvals; and there was no indication that any sponsor had informed FDA that such submission would be forthcoming. It was also determined at that time that MDMA is not a grandfathered drug and that it has not been approved for over-the-counter use. (Tocus, direct, p. 5, 6, 9)

13. On June 6, 1984, the Acting Assistant Secretary for Health sent a letter to the Administrator of DEA which stated that a scientific and medical evaluation of MDMA had been completed. He further recommended that MDMA be placed in Schedule I of the CSA.

Attached to the letter was an "Evaluation of the DEA Recommendation to Control MDMA in Schedule I of the CSA." In this evaluation, the Acting Assistant Secretary for Health stated that he concurred with DEA's recommendation of Schedule I for MDMA. The evaluation included a list of the findings required to be made for Schedule I substances, which included the finding that the drug has no currently accepted medical use in treatment in the United States. The evaluation of the Acting Assistant Secretary for Health stated that he concurred with this finding. (A-B3, A-B4)

Discussion

The phrase "currently accepted medical use in treatment in the United States" is found in 21 U.S.C. § 812(b) as one of three findings required to be made by the Administrator of the Drug Enforcement Administration for placement of a substance in any of the five schedules created by the Controlled Substances Act. For placement in Schedule I, a finding that "the drug or other substance has no currently accepted medical use in treatment in the United States" is required. (21 U.S.C. § 812(b)(1)(B)) For the other four schedules, the finding is "the drug or other substance has a currently accepted medical use in treatment in the United States." That phrase is further qualified for Schedule II substances by the addition of "or a currently accepted medical use with severe restrictions."

The phrase "currently accepted medical use" is not found in any of the drug control legislation which preceded the Controlled Substances Act. The narcotic control legislation specifically

designated drugs which were subject to control and authorized the Secretary of Treasury to designate substances as opiates based upon their chemical similarity to narcotics already listed and their "addiction-forming or addiction-sustaining liability." 15/ The Drug Abuse Control Amendments to the Federal Food, Drug and Cosmetic Act which were found, prior to repeal, at 21 U.S.C. § 321 et seq. make no reference to medical use. Classification under that Act was conducted by the Secretary of the Department of Health, Education and Welfare, and was based upon the drug's potential for abuse and pharmacology. The phrase "accepted medical use" is currently found in no other Federal statute.

The legislative history of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (Pub. L. 91-513) and specifically the scheduling provisions of Sections 201 and 202 (21 U.S.C. §§ 811 and 812), provide scant reference to and no specific definition of the term "accepted medical use." During the hearings on the Act, Dr. John Jennings, then Acting Director of the Bureau of Drugs, Food and Drug Administration, testified before the House of Representatives Subcommittee on Public Health and Welfare on February 19, 1970. In response to a question asking if a substance currently under an investigational new drug application had an "accepted medical use" he stated that when a drug is in an investigational status, the drug would usually not have any accepted medical use because "medical use has not been established." [Emphasis added]

15/ Subsection (g) of Section 4731, Internal Revenue Code of 1954 [Repealed by Pub. L. 91-513]

In 1984, Congress ordered the Drug Enforcement Administration to transfer the drug methaqualone from Schedule II to Schedule I of the Controlled Substances Act. 16/ The legislation also ordered the Secretary of Health and Human Services to withdraw approval of the new drug application for methaqualone. The Report of the House Committee on Energy and Commerce which accompanied H.R. 4201 stated:

> The Drug Enforcement Administration does not have authority to impose Schedule I controls on a drug which has been approved by the Food and Drug Administration for medical use. 17/

Congress recognized that approval by the Food and Drug Administration was necessary to demonstrate accepted medical use, and that the approval was the approval of a new drug application. By ordering the Secretary to withdraw the NDA for methaqualone, Congress ensured that the drug then met all the criteria for control in Schedule I, particularly that it had "no currently accepted medical use in treatment in the United States."

In 1970, the same year in which the Comprehensive Drug Abuse Prevention and Control Act was passed by Congress, the Uniform Controlled Substances Act was drafted by the National Conference of Commissioners on Uniform State Laws. In the prefatory note to the Uniform Controlled Substances Act, the Commissioners explained the purpose of the uniform act;

> This Uniform Act was drafted to achieve uniformity between the laws of the several States and those of the Federal government. It has been designed to

16/ Pub. L. 98-329

17/ H.R. Rep. No. 98-534, 98th Cong., 1st. Sess. 4 (1983)

> complement the new Federal narcotic and dangerous drug legislation and provide an interlocking trellis of Federal and State law to enable government at all levels to control more effectively the drug abuse problem.
>
> The main objective of this Uniform Act is to create a coordinated and codified system of drug control, similar to that utilitzed at the Federal level, which classifies all narcotic, marihuana, and dangerous drugs subject to control into five schedules, with each schedule having its own criteria for drug placement. This classification system will enable the agency charged with implementing it to add, delete, or reschedule substances based upon new scientific findings and the abuse potential of the substance.

The Uniform Controlled Substances Act has been adopted by almost all of the fifty states. The commentary to this act makes it clear that the phrase "accepted medical use in treatment in the United States as used in the Uniform Act, means accepted by the Food and Drug Administration as safe and effective. (See finding of fact number 3.) Controlled substance scheduling authorities in thirty-five states which responded to a survey conducted by Mr. David Joranson indicated that their interpretation of the meaning of accepted medical use was consistent with that stated by the Commissioners in their comment.

The Federal Food, Drug and Cosmetic Act was enacted in 1938. It contains provisions regarding approval of drugs for marketing in the United States and an exemption for investigational use of unapproved drugs prior to marketing. The provisions for an exemption for investigational use are found in the statute at 21 U.S.C. § 355(i). This section gives the Secretary authority to promulgate regulations

for the investigational use of new drugs. The statute lists three conditions "relating to the protection of the public health" to be included by the Secretary in the regulations. The listed conditions require that investigators submit to FDA "preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing," that all investigators provide a signed agreement that, "patients to whom the drug is administered will be under his personal supervision, or under the supervision of investigators responsible to him," that the investigator maintain records and make reports to the Secretary, and that all human beings or their representatives to whom the drug is administered be advised that the drug is investigational. 18/ The regulations which have been implemented to this statutory provision are found at 21 C.F.R. § 312 and contain extensive requirements for the use of unapproved drugs for investigational purposes. The Federal Food, Drug and Cosmetic Act and its implementing regulations provides very specific and comprehensive requirements to be satisfied by those who use unapproved drugs for investigational purposes. In 21 U.S.C. § 355(i) Congress has specifically defined those who will be conducting the investigations as, "experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs."

This system of approval of new drugs and exemptions for investigational use had already been in place for many years prior to the enactment of the Controlled Substances Act. Indeed, the Drug Abuse Control Amendments, controlling certain dangerous drugs, were

18/ 21 U.S.C. § 355(i)

part of the Federal Food, Drug and Cosmetic Act. There is no doubt that these two statutes are related. In commenting on the interrelationship of these two statutes and the Food and Drug Administration's role in drug marketing, Judge Pratt of the United States District Court for the District of Columbia found in American Pharmaceutical Association v. Weinberger, that

> The Court concludes that Congress intended to create two complementary institutional checks on the production and marketing of new drugs. At the production or pre-marketing state, the FDA is given the primary responsibility in determining which new drugs should be permitted to enter the flow of commerce. The Commissioner must approve or deny every NDA, or he may determine that a particular new drug qualifies for IND status in order to permit additional experimentation. When an IND exemption is approved, the Commissioner may, of course, severely restrict the distribution of the exempted drug to bona fide researchers and clinicians. 19/

The relationship between the Food, Drug and Cosmetic Act and the Controlled Substances Act is futher reinforced by cross references in the CSA to the Food, Drug and Cosmetic Act. For example, the CSA states, "The term 'drug' has the meaning given that term by section 321(g)(1) of this title." 20/ Section 321(g)(1) of Title 21 is in the definition section of the Food, Drug and Cosmetic Act. Labeling and prescription requirements of the Controlled Substances Act make reference to the Food, Drug and Cosmetic Act. See: 21 U.S.C. § 825 and 21 U.S.C. § 829. In addition, there are numerous references to the "Secretary" in various sections of the CSA which "means the

19/ 377 F. Supp. 824, 830 (D.D.C. 1974)

20/ 21 U.S.C. § 802(12)

Secretary of Health and Human Services." 21/

Since the Food, Drug and Cosmetic Act and the Controlled Substances Act are related to one another, it follows that when addressing the meaning of the phrase "accepted medical use in treatment in the United States," both statutes must be examined. The phrase is not specifically defined in either statute; however, the Food, Drug and Cosmetic Act does provide a mechanism for "approval" of drugs prior to marketing. This is the only official act by any government agency which could be linked to acceptance of a substance for medical use.

If a substance is not marketed in interstate commerce in the United States, it is not widely available for use by the vast population of physicians in this country who prescribe and dispense drugs in the course of their medical practice. It is not manufactured by a pharmacuetical manufacturer licensed by FDA to manufacture drugs, it is not sold by pharmaceutical wholesalers, it is not stocked in retail pharmacies or hospitals. Therefore, the average physician in the United States, of which there were an estimated 505,000 in 1981, 22/ would not have access to the drug. Although no estimate of the number of physicians using MDMA was introduced during the proceedings, there is no evidence that it is widely used by physicians across the country.

21/ 21 U.S.C. § 802(24)

22/ Statistical Abstract of the United States 1984, U.S. Dept. of Commerce, Bureau of Census

The complex system of approval for marketing and conditions for use of nonapproved drugs for investigational purposes is to protect the health of the humans to whom the drug is to be given. A drug must be shown to be safe and effective before any manufacturer can market it in this country. Approval of a substance makes it "acceptable" and available for medical use. Any other meaning of "currently accepted medical use in treatment in the United States" other than approval for marketing by the Food and Drug Administration would make the NDA process a sham and would require pure conjecture on the part of the Secretary and the Administrator in determining if a substance had an "accepted medical use."

There is no evidence in the record that MDMA is being used by any more than a handful of physicians. None of them have applied to FDA for an IND. MDMA has not been approved for marketing in the United States. It has no approved new drug application (NDA). It has no approved investigational new drug application (IND). MDMA may not be administered to human subjects without the approval of the Food and Drug Administration. This approval requires the submission of an IND which must contain data showing that the drug will not cause irreversible damage in humans. The Department of Health and Human Services, through the FDA, has concluded that there is no currently accepted medical use of MDMA in the United States based upon a review of its files. There is no conceivable standard by which MDMA could be considered to have an "accepted medical use in treatment in the United States."

Conclusions of Law

The phrase "currently accepted medical use in treatment in the United States" as used in 21 U.S.C. § 812 means that the Federal Food and Drug Administration has determined that a drug or other substance can be lawfully marketed in the United States.

Since it has not been determined that MDMA may be lawfully marketed in the United States, MDMA has no currently accepted medical use in treatment in the United States.

ACCEPTED SAFETY FOR USE UNDER MEDICAL SUPERVISION

Two of the issues in this proceeding concern the concept of "accepted safety for use . . .under medical supervision." Issue number three addresses the meaning of the phrase as used in Section 812 of Title 21 United States Code, and issue number six addresses whether there is a "lack of accepted safety for use . . .under medical supervision" of MDMA. Both of these issues will be discussed in this section.

Findings of Fact

1. The Food and Drug Administration evaluates the safety of a substance throughout the investigational new drug (IND) process, and as part of the new drug application (NDA) approval status. (Tocus, direct, p. 2, 3)

2. The sponsor of an IND is responsible for supplying FDA with the results of preclinical (animal) studies which show that there will be no unreasonable hazards in initiating studies in humans with the drug. At a minimum, these initial studies must include a

pharmacological profile of the drug, acute toxicity studies in several species, and short term toxicity studies ranging from 2 weeks to 3 months. (Tocus, direct, p. 2, GG-6)

3. A substance is not deemed "safe" by the Food and Drug Administration unless FDA, after a review of scientific data submitted during the IND process, has determined that the substance can be given to humans without irreversible harm. (Tocus, direct, p. 9)

4. No scientific data was supplied to the Food and Drug Administration which would demonstrate the safety of MDMA, and a review of the scientific literature led an FDA official who evaluates the safety and efficacy of drugs to conclude that the literature does not support the safety of MDMA for use under medical supervision. (Tocus, direct, p. 9)

5. On June 29, 1982, the Food and Drug Administration (FDA) published in the Federal Register "Proposed Recommendations to the Drug Enforcement Administration Regarding the Scheduling Status of Marihuana and Its Components and Notice of a Public Hearing" (47 FedReg. 28141) in which the Commissioner of Food and Drugs stated,

> the Federal Food, Drug and Cosmetic Act provides that FDA approve an NDA upon scientific evidence that the drug has been shown to be safe and effective for its proposed uses. See 21 U.S.C. 355(d). Becuase no drug is ever completely safe in the absolute sense, FDA considers "safe" to mean (in the context of a human drug) that the therapeutic benefits to be derived from the drug outweigh its known and potential risks under the conditions of use in labeling. . .
>
> Another factor considered by FDA in assessing the drug's safety is the proposed labeling which is approved at the time of approval for marketing. A drug might be considered safe for some proposed uses but not others. Only those proposed uses

> where the benefit/risk ratio is favorable will be included in the indications section of the drug's labeling. . .
>
> But it is only upon approval for marketing, when there has been an institutional decision based upon scientific judgement by the regulatory agency charged with the responsibility of evaluating the safety and efficacy of new drugs, that a drug becomes "accepted" as safe under medical supervision. (47 Fed. Reg. 28152)

(A-B14)

6. There is no legitimate commercial manufacturer of MDMA in the United States. Further the MDMA which has been used by the psychiatrists is not labeled with safety or therapeutic considerations. (A-B2, T-7, p. 38)

Discussion

The Federal Food, Drug and Cosmetic Act requires a showing of safety and efficacy prior to approval of a new drug application (NDA). The statute requires that an application for a new drug application contain the following:

> (1) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (2) a full list of the articles used as components of such drug; (3) a full statement of the composition of such drug; (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (6) specimens of the labeling proposed to be used for such drug. 23/

Even before a new drug is approved for investigational use in humans, the investigator must show FDA that the drug will not produce irreversible harm to humans. This must be shown through scientifically designed and reliable animal toxicity studies which are evaluated by the Food and Drug Administration. Once this

23/ 21 U.S.C. § 355(b)

threshold level of safety is established and an IND is approved, the investigator may proceed with very limited clinical studies which are designed to determine the effectiveness of the substance and the specific conditions under which the substance may be safely used. These conditions are ultimately listed in the labeling of a substance if it is approved for marketing. It is critical that the preclinical and clinical studies used to establish both the safety and efficacy of a substance are controlled, reliable scientific studies and that these studies are submitted to the Food and Drug Administration for evaluation on an ongoing basis. In Edison Pharmaceutical v. Food and Drug Administration, a case concerning the review of an FDA refusal to approve a new drug application, the United States District Court for the District of Columbia (Tamm, J.) stated that

> Section 505(d)(1) of the Act, 21 U.S.C. § 355(d)(1) (1976) requires that an NDA include "adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof.". . . Although the Commissioner [of FDA] recognized that studies showing the safety of a drug need not be adequate and well-controlled withing the meaning of 21 C.F.R. § 314.111(a)(5), he properly ruled that they "must be adequately constructed so that scientists can draw reasonable conclusions from them. 24/

The court further concluded that

> Edison's attempt to replace evidence of "controlled" investigation with testimony relating personal experiences or clinical impressions is inconsistent with the Act, the accompanying regulations, and explicit Supreme Court precedent. 25/

24/ 600 F. 2nd. 831, 840 (D.C. Cir. 1979)

25/ 600 F. 2nd 831, 842 (D.C. Cir. 1979)

A drug's safety for use in humans, both at the investigational stage and at the marketing approval stage can only be established through controlled scientific studies which are submitted to any evaluated by the Food and Drug Administration.

In Weinberger v. Hynson, Westcott & Dunning, Inc., the Supreme Court discussed the standards required by the Food and Drug Administration to demonstrate the efficacy of a drug

> Moreover, their strict and demanding standards, barring anecdotal evidence indicating that doctors "believe" in the efficacy of a drug, are amply justified by the legislative history. The hearings underlying the 1962 Act show a marked concern that impressions or beliefs of physicians, no matter how fervently held, are treacherous. 26/

The same rationale discussed with regard to "accepted medical use" applies to "accepted safety for use . . .under medical supervision." The Food, Drug and Cosmetic Act and the Controlled Substances Act are related statutes. They must be read together. The Department of Health and Human Services plays an important role in the scheduling of substances under the Controlled Substances Act. They are charged with making medical and scientific determinations regarding control of a drug or other substance. Those determinations are binding upon the Administrator of DEA. Since the Food and Drug Administration has a highly sophisticated mechanism available for evaluating the safety and efficacy of drugs, that standard is the one which is "accepted."

Congress could not have intended the Administrator of the Drug Enforcement Administration to make such a determination, in an area so vitally important to the health and safety of the public, on less than reliable scientific data. The anectodal reports of individuals

26/ 412 U.S. 609, 619 (1973)

who have taken the substance, and their observations of others who have taken a drug are not enough for the Food and Drug Administration to find a drug "safe," even if they had been submitted to FDA for review. The Administrator certainly cannot find a drug or other substance to be "safe" based upon such evidence.

MDMA has not been approved for marketing in the United States by the Food and Drug Administration. MDMA has not been approved for investigational use by the Food and Drug Administration. No studies have been submitted to the Food and Drug Administration which would demonstrate the safety of MDMA with reliable scientific data. There is no basis upon which to conclude that MDMA has "accepted safety for use . . . under medical supervision."

Conclusions of Law

The phrase "accepted safety for use . . . under medical supervision" as used in 21 U.S.C. § 812(b) means that a drug has been evaluated for safety by the Food and Drug Administration and approved for marketing in the United States. Since MDMA has not been evaluated for safety by the Food and Drug Administration, and has not been approved for marketing in the United States, it does not possess "accepted safety for use. . . under medical supervision."

EFFECT OF FINDINGS OF THE SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES

Issue number four in this proceeding addresses whether a finding by the Secretary of the Department of Health and Human Services that a substance has "no currently accepted medical use in treatment in the United States" or a finding that a substance has no "accepted safety for use . . . under medical supervision" is binding on the Attorney General (Administrator) within the purview of the provisions of 21 U.S.C. § 812.

The statutory language of 21 U.S.C. § 812 is clear that

> The recommendations of the Secretary to the Attorney General shall be binding on the Attorney General as to such scientific and medical matters . . .

The question then becomes whether "accepted medical use" of a drug or other substance, and "accepted safety for use . . . under medical supervision" of a drug or other substance, are scientific and medical matters to be determined by the Secretary. Since these determinations are clearly scientific and medical matters, such recommendations are indeed binding on the Attorney General (Administrator).

The legislative history of the Comprehensive Drug Abuse Prevention and Control Act of 1970 contains much discussion of the role of the Department of Health and Human Services (at that time called the Department of Health, Education and Welfare) and the role of the Justice Department in control actions conducted pursuant to 21 U.S.C. §§ 811 and 812. This was explained in House Report No. 91-1444, 91st. Cong., 2d Sess. as follows:

> Considerable controversy arose during the hearings over this provision of the bill, with respect to the proper role of the Attorney General and the Secretary of Health, Education, and Welfare in making determinations concerning which drugs should be controlled. The reported bill strikes a balance between the extent to which control decisions should be based on law enforcement criteria, and the extent to which such decisions should be based on medical and scientific determinations. The bill provides the ultimate authority for decision as to whether or not drugs should be controlled, and the schedule in which they are to be placed, shall rest with the Attorney General, based upon all the evidence, with all scientific and medical determinations being made by the Secretary of Health, Education, and Welfare, and these determinations being made binding upon the Attorney General. 27/

Congress made it clear in enacting the statute in its present form, that although the Attorney General will have the final authority in making control decisions, the Secretary was to play a major role, and that role was to be with respect to scientific and medical matters. The Attorney General was to address primarily "law enforcement criteria."

The legislative history further discusses the factors which the Secretary must consider in making his evaluation and recommendation to the Attorney General, and reiterating that the Secretary's evaluations and recommendations are binding on the Attorney General. The factors which the Secretary must consider are listed in 21 U.S.C. § 811(c) and include;

> the substance's pharmacological effect, the state of current knowledge regarding the substance, the risk to the public health posed by the substance, the substance's psychic or physiological dependence liability, and whether or not the substance is an immediate precursor of a substance already controlled. 28/

27/ [1970] U.S. Code Cong. & Admin. News 4589

28/ Id. p. 4600

Whether the substance in question has a "currently accepted medical use in treatment in the United States" is certainly a medical and also a scientific finding. It has to do with the drug approval process outlined in the Federal Food, Drug and Cosmetic Act. It deals with the pharmacology of the drug, the safety of the drug for specific uses, and the efficacy of the drug. The current knowledge of the substance and the risk to the public health posed by the substance are certainly matters that are dealt with in detail by the Food and Drug Administration in the course of the drug approval process. Information concerning medical use and safety for use are intimately related to the safety and efficacy of a drug for therapeutic purposes.

Congress clearly divided the areas of consideration into law enforcement criteria and scientific and medical matters. Whether a substance is currently accepted for medical use in the United States, and whether a substance is safe for use under medical supervision are logically not law enforcement matters. By clear process of elimination, they are scientific and medical issues.

PHARMACOLOGICAL PROFILE AND POTENTIAL FOR ABUSE OF MDMA

The seventh issue to be addressed in this matter is, "If on the basis of the resolution of the above issues, MDMA can lawfully be scheduled in a schedule other than Schedule I, in which schedule should it be placed?" Since the "above issues" refer to the previously discussed matters of whether MDMA has a "currently accepted medical use in treatment in the United States" and whether

MDMA "lacks accepted safety for use. . . under medical supervision," the only finding required to be made by the Administrator which has not been addressed is potential for abuse of MDMA.

The phrase "potential for abuse" was discussed in extensive detail in the legislative history of the Controlled Substances Act. That discussion was presented under the topic, "scheduling criteria" which was presented earlier in this document. Although Congress defined and discussed potential for abuse, there is no specific guidance in the Act or legislative history as to how relative potential for abuse should be determined. In passing the Controlled Substances Act, Congress placed specific drugs into each of five schedules; a consideration of the relative potential for abuse must have played a major role in the placement of these drugs in their respective schedules. Substances placed into Schedules I and II by definition have a high potential for abuse. The other schedules have lower potential for abuse than the next higher schedule; e.g. Schedule III substances have a lower potential for abuse than Schedule I or II, but higher than Schedule IV.

One of the criteria listed in the legislative history for potential for abuse is that a drug or other substance is so related in its action to a drug already scheduled that it is likely that the drug will have the same potential for abuse as the substance that is already scheduled. Thus, relative potential for abuse must be based, to a large degree, on the pharmacological activity of the substance in question as compared to that of a substance or substances with known abuse potential.

Several terms regarding pharmacological activity and classification of substances into certain pharmacological categories have been used throughout this proceeding. The terms "stimulant" or "amphetamine-like" and "hallucinogenic" were commonly used in the proceeding. The Controlled Substances Act defines the term "depressant or stimulant substance" as

> (A) a drug which contains any quantity of (i) barbituric acid or any of the salts of barbituric acid; or (ii) any derivative of barbituric acid which has been designated by the Secretary as habit forming under section 352(d) of this tile; or
>
> (B) a drug which contains any quantity of (i) amphetamine or any of its optical isomers; (ii) any salt of amphetamine or any salt of an optical isomer of amphetamine; or (iii) any substance which the Attorney General, after investigation, has found to be, and by regulation designated as, habit forming because of its stimulant effect on the central nervous system; or
>
> (C) lysergic acid diethylamide; or
>
> (D) any drug which contains any quantity of a substance which the Attorney General, after investigation, has found to have, and by regulation designated as having, a potential for abuse because of its depressant or stimulant effect on the central nervous system or its hallucinogenic effect. 29/

Paragraph (D) above is language which was found in the regulations implementing the Drug Abuse Control Amendments (DACA) of 1965 at 21 C.F.R. § 166.2(e). Nowhere in the current Act or regulation are the terms stimulant and hallucinogenic defined. To determine the legislative meaning of these terms, the regulations issued pursuant to the DACA 1965 which specifically define these terms must be examined.

29/ 21 U.S.C. §802(9)

In 1968, the Director of the Bureau of Narcotics and Dangerous Drugs published a regulation in the Federal Register (33 Fed. Reg. 14842) which became 21 CFR § 320.2. This regulation listed factors which the Director should consider in determining whether a drug had a stimulant, depressant, or hallucinogenic effect. With regard to stimulant effect, the regulation stated:

> (a) In determining whether a drug has a "stimulant effect" on the central nervous system, the Director will consider, among other relevant factors, whether there is substantial evidence that the drug may produce any of the following:
> (1) Extended wakefulness
> (2) Elation, exhilaration, or euphoria (exaggerated sense of well-being)
> (3) Alleviation of fatigue.
> (4) Insomnia, irritability, or agitation.
> (5) Apprehension or anxiety.
> (6) Flight of ideas, loquacity, hypomania, or transient deliria.

The same regulation continues by defining the term hallucinogenic effect as follows:

> (b) In determining whether a drug has a "hallucinogenic effect," the Director will consider, among other relevant factors, whether there is substantial evidence that it may produce hallucinations, illusions, delusions, or alteration of <u>any</u> of the following:
>
> (1) Orientation with respect to time or place.
> (2) Consciousness, as evidenced by confused states, dreamlike revivals of past traumatic events, or childhood memories.
> (3) Sensory perception, as evidenced by visual illusions, synesthesia, distortion of space and perspective.
> (4) Motor coordination.
> (5) Mood and affectivity, as evidenced by anxiety, euphoria, hypomania, ecstasy, autistic withdrawal.
> (6) Ideation, as evidenced by flight of ideas, ideas of reference, impairment of concentration and intelligence.
> (7) Personality, as evidenced by depersonalization and derealization, impairment of conscience and of acquired social and cultural customs.

Potential for abuse is shown by demonstrating that the drug or

substance in question is chemically and pharmacologically related to a substance with a known potential for abuse. It is also shown by demonstrating that individuals are taking the substance on their own initiative rather than pursuant to medical advice, or that they are taking the substance in amounts sufficient to create a hazard to their health or the safety of the community.

The chemistry, pharmacology, toxicology, abuse liability, and actual abuse of MDMA and related compounds with known high abuse potential will be described in the following findings of fact.

Findings of Fact

1. MDMA or 3,4-methylenedioxymethamphetamine belongs to a class of compounds which can be termed phenethylamines or narrowly defined, phenylisopropylamines or amphetamines. (GG-25, p. 839; GG-31, p. 259, 277, 288, 291, 292; GG-9, p.1)

2. MDA or 3,4-methylenedioxyamphetamine, amphetamine and methamphetamine are also phenylisopropylamines. (A-B2, p. 4)

3. MDA, or 3,4-methylenedioxyamphetamine is formed by the addition of a methylenedioxy group to amphetamine. (A-B2, p. 4; GG-4)

4. MDMA is formed by the addition of a methylenedioxy group to methamphetamine. (A-B2, p. 4; GG-4)

5. The addition of a methylenedioxy group to the aromatic nucleus of amphetamines produces compounds with psychotomimetic activity. (A-A3, GG-4, GG-25, GG-31)

6. Psychotomimetic is a term used to describe a large class of compounds which change or modify a person's mood or mental state. (GG-31, p. 243) The terms psychotomimetic and hallucinogenic are

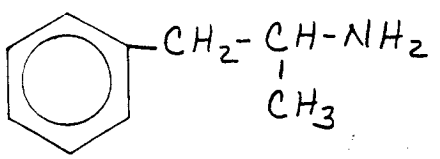
commonly used interchangeably. (GG-25, p. 839)

7. MDMA is the N-methyl analog of MDA. This means that MDMA differs structurally from MDA the same way that methamphetamine differs from amphetamine, by the addition of an N-methyl group. (Sapienza, direct, p.5; A-B2, Tocus, direct, p. 8)

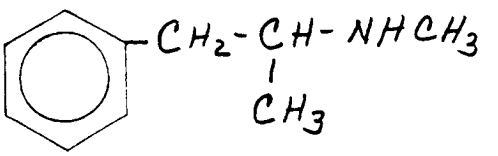
8. N-methylation of MDA yields MDMA which retains the psychotomimetic properties of MDA. (A-A3, GG-4, GG-25, GG-31, Vaupel, T-6, p. 137)

9. N-methylation of amphetamine yields methamphetamine which retains the central nervous system activity of amphetamine. (A-B2, p. 4; GG-4, p. 193; GG-5; Hardman, direct, p. 4)

10. The difference in structure between amphetamine and methamphetamine is illustrated by the following diagram:



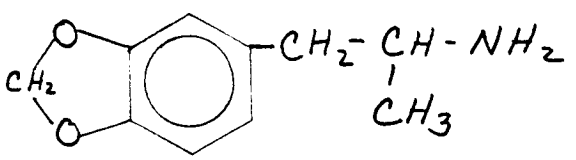
amphetamine



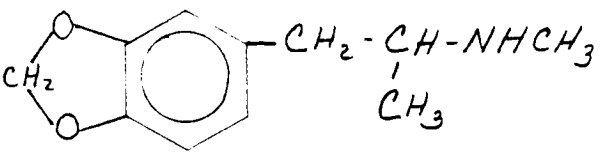
methamphetamine

(A-B2, p. 5)

11. The difference in structure between MDA and MDMA is illustrated by the following diagram:



MDA



MDMA

(A-B2, p. 9)

12. MDMA produces pharmacological effects in common with both central nervous system stimulants like amphetamine, and hallucinogens like MDA in animals. (A-B2, A-B4, A-B27, A-A5, A-A4, GG-24, GG-40)

13. MDA and MDMA both produce central nervous system stimulation as measured by increased locomotor activity in mice. (A-A4, A-A5, A-B23, GG-40)

14. Tests conducted by Braun, Shulgin and Braun show that at an oral dose of 20mg/kg in mice, MDA produced a significant increase in locomotor activity. At the same dose, MDMA produced approximately three times the motor activity of MDA during the first three hours after application. They concluded that MDA, MDMA and N-ethyl MDA caused the greatest stimulation and that this is consistent with results of tests in mice of amphetamine compounds with no ring substitution (e.g. amphetamine and methamphetamine). Braun, Shulgin and Braun further conclude that "compounds which cause a sharp increase in motor activity in animals generally prove to have a pronounced central nervous system effect in man. (GG-5, A-A4)

15. A study conducted by Intox Laboratories reported significantly reduced body weights at 7 and 14 days following initiation of MDMA dosing in rats. (GG-40)

16. The Intox Laboratory study also reported that rats who had been administered MDMA showed hyperactivity, excitability, aggressive behavior and stereotypic behavior. (GG-40)

17. Studies conducted by Dr. Harris at the Medical College of Virginia compared the locomotor activity in mice using d-amphetamine

and MDMA. Dr. Harris found that MDMA produces slightly less central nervous system stimulation than amphetamine at peak activity which is 1 1/2 hours after administration. However, at 5-15 minutes and 2-3 hours after administration, the maximum stimulating effect of MDMA is substantially greater than that produced by d-amphetamine. (A-B23)

18. MDA and MDMA produce similar centrally mediated analgesic effects in mice as determined by the hot-plate test, the tail-flick test and the stretch test. The tail-flick test and hot plate tests showed that MDMA produces an increased analgesic effect over that produced by MDA. (A-A4)

19. MDA and MDMA both produce an increase in body temperature when administered to rabbits at similar potencies. (A-A1) Hyperthermia in rabbits is reported to be a measure of central nervous system activity. (A-A1, GG-25) Dr. Shulgin notes that there is a reasonably good parallel between the hyperthermia response in rabbits and some of the effects of LSD, and that these parallel quite closely the psychopharmacological potency in humans. He feels that it is probably the best animal test at present for estimating psychotomimetic potency. (GG-31, p. 253)

20. Both MDA and MDMA are potent releasers of serotonin or 5-hydroxytryptamine, a neurotransmitter which has a widely accepted role in the activity of hallucinogens. (GG-27; Nichols, T-3, p. 140; Kleinman, direct, p. 3)

21. In mice, dogs and monkeys, MDA and MDMA produce the same spectrum of pharmacological effects when observed during toxicity studies. (A-A7, GG-40) These effects include hyperactivity,

excitability, emesis, apprehension or fright, aggressive behavior, bizarre body attitudes, apparent hallucinations, dyspnea and hyperpnea. Motor activity effects include convulsions, muscular rigidity and tremors and the autonomic activity includes mydriasis, piloerection, salivation and vascular flushing (A-A5, A-A7, GG-40, Hardman, direct, p. 2) These effects are part of what is described as the classical pharmacological response of the dog to intravenous mescaline. (A-A7; Hardman, direct, p. 2)

22. The lethality of a compound is reported as an LD50, which is the dose of a drug which will kill 50% of the animals treated with that dose. (Hardman, T-6, p. 17)

23. The LD50's for mescaline, MDA and MDMA were determined by intravenous or intraperitoneal administration in five species of animals. MDMA had LD50's between 2 and 6 times less than those of mescaline and between 1.5 and 3 times more than MDA. This means that MDMA is more lethal than mescaline but less lethal than MDA. (Hardman, direct, p. 2; A-A7)

24. Intraperitoneal LD50's for MDA and MDMA were determined in mice by Davis. (A-A5) The LD50's of MDMA and MDA were substantially the same with the LD50 for MDA equalling 90.0 mg./kg. and the LD50 for MDMA equalling 106.5 mg./kg. Dr. Hardman found the LD50 of MDA to be 92 mg./kg. (A-A5, A-A7) Davis also found that both MDA and MDMA showed the amphetamine-like property of increased lethality under aggregated housing conditions compared to isolated housing conditions. (A-A5)

25. In the study conducted by Intox Laboratories the oral LD50

for MDMA in rats was estimated to be approximately 325 mg./kg. (GG-40) No oral value was reported for MDA but based on the data from Intox Laboratories, Dr. Hardman estimated it to be approximately 150 mg./kg. (Hardman, T-6, p. 51)

26. MDMA, MDA, amphetamine and methamphetamine produce neurotoxic effects when administered to animals. (Seiden, direct, p. 2, 3, exhibits 2, 3, 4, 7, 8, 9, 10; A-B2; A-B24) MDMA and MDA are neurotoxic in rats at doses which are very low compared to the neurotoxic doses of amphetamine and methamphetamine (Seiden, direct, p. 3, 4; Seiden, T-3, pp. 87, 88, 91, 94)

27. MDMA and MDA both produce long term reduction in serotonin levels and serotonin uptake sites in the rat brain. (Seiden, direct, exhibit 10; A-B22, A-B24) These neurochemical depletions are due to the destruction of serotonin nerve terminals as determined by visual staining techniques (Seiden, direct, p. 3, exhibit 10; A-B22, A-B24; Seiden, T-3, pp. 64, 65, 68, 71, 79)

28. In humans, serotonin nerve terminals are believed to play a major role in mood, emotion, pain perception, sleep and affect the regulation of aggressive and sexual behavior. (Seiden, direct, p. 1; Kleinman, direct, p. 3)

29. Although single injections of MDMA may be slightly less neurotoxic than MDA, chronic use of MDMA appears to be more neurotoxic than MDA (A-B24)

30. The neurotoxicity of amphetamine and methamphetamine has been determined in rats, guinea pigs and monkeys. (Seiden, direct, p. 3, exhibit 4)

31. MDMA and MDA are likely to produce the same neurotoxic effects to serotonergic nerves in humans. (Seiden, direct, p. 4; Seiden, T-3, pp. 84, 85; A-B24) The neurotoxicity of MDMA may have an effect on individuals taking as little as 100-200 milligrams of the drug or taking multiple doses. (Seiden, direct, p.4; A-B24)

32. Drug discrimination studies in animals allow one to determine if a particular dose of a test substance produces effects which are recognized as the same as those produced by a particular dose of a another substance. (Glennon, direct, p. 1, T, p. 8) It is believed that the effects recognized by the animals in these studies are central nervous system effects and hence this paradigm is very useful in characterizing centrally acting compounds. (Glennon, deposition, p. 10, 12, 14, 15)

33. If a test drug in animal drug discrimination studies elicits similar responses to a standard drug, both the test drug and the standard drug are assumed to have similar abuse potential if the reinforcing properties and adverse effects of the standard and test drugs are similar. (A-B21, article 1, p. 138)

34. In drug discrimination paradigms, complete generalization indicates that the test compound is similar enough for the animal to recognize it as the training drug by responding on the appropriate drug lever at least 80% of the time. No generalization indicates that the test compound is unlike the training compound so that a low number of responses will be made on the drug lever. Partial generalization indicates that there may be pharmacological effects common to both test and training drug, but that some doses of the

test and training drug are similar and at the tested doses another type of pharmacological effect may predominate. (Glennon, direct, exhibit 2, pp. 70-74; GG-28; Nichols, T-3, pp. 147-150)

35. MDMA shares discriminative stimulus properties in common with amphetamine and MDA in drug discrimination studies in rats. (Glennon, direct, pp. 2, 3; A-A6)

36. In a drug discrimination test described by Dr. Glennon, rats trained to recognize amphetamine also recognized MDA and MDMA. MDMA was slightly more potent than MDA in being recognized as amphetamine. Other compounds which generalized to the amphetamine stimulus included methamphetamine, cocaine and para-methoxyamphetamine. (Glennon, direct, pp. 1, 2, 3)

37. Rats trained to recognize MDA recognized MDMA in drug discrimination studies conducted by Dr. Glennon. (A-A6; Glennon, direct, p. 2; Nichols, T-3, pp. 155, 156)

38. MDA completely generalized (83% correct response) in rats trained to recognize 4-methyl-2,5-dimethoxyamphetamine (DOM), a substance with known hallucinogenic properties, but only within a very narrow dosage range. (GG-9; Glennon, direct, exhibit 2, pp. 83, 84, table 6)

39. MDMA showed partial generalization (52% correct response) in rats trained to recognize DOM, at a specific dose. (GG-10, table 1)

40. A standard abuse liability test for assessing the reinforcing properties of a drug is the substitution procedure. It is the most common and reliable method for determining whether a drug will be self-administered. In this procedure new drugs are tested to

determine whether or not they will maintain the responding of animals trained to lever press for intravenous delivery of a known drug reinforcer. (A-B23, p. 3; A-B21, article 3, p. 165)

41. In tests conducted with rhesus monkeys and baboons trained to self-administer cocaine, the monkeys and baboons continued to self-administer when MDMA was substituted for the cocaine. (A-B21, A-B23)

42. Of three baboons that self-administered MDMA, two exhibited unusual behavior. One appeared to track nonexistent objects, and another exhibited aggressive behavior. Levels of self administration in all three baboons tested were in the same range as those of MDA and slightly less than those of cocaine, amphetamine and phencyclidine. (A-B21)

43. Drs. Shulgin and Nichols first reported that MDMA produces psychotomimetic effects in man in 1976. (GG-35, A-B2) These effects are described as intoxication, altered state of consciousness and sympathomimetic stimulation. (GG-35)

44. The racemic mixture of MDMA, which is a combination of both optical isomers, is the drug which is clandestinely produced, found in the illicit traffic and used by psychiatrists. (Sapienza, direct, p. 6, Nichols, T-3, p. 129)

45. In a 1978 publication, Dr. Shulgin reported that racemic MDMA produced a high level of intoxication in man at doses of 100-160mg. Color enhancement as well as physical symptoms of mydriasis and jaw clenching were noted. MDMA was described as maintaining the same potency as MDA but exhibiting subtle differences in the

qualitative nature of the intoxication. (A-A1, GG-1)

46. In a 1980 publication, Dr. Shulgin and others describe MDA and MDMA as having both stimulant and psychotomimetic properties in humans. Racemic MDA and MDMA were administered orally to five volunteers at doses up to 160mg. The effective dose of MDA was 60-120mg., while that of MDMA was 100-160mg. Dr. Shulgin and others noted a drive increasing effect, a change in expression and an apparent increase in the acoustic, visual and tactile sensory perceptions as well as a tension-decreasing, mood-lightening effect in the human subjects. Mydriasis and sympathomimetic stimulation were noted during the entire period. The effects of MDA and MDMA were apparent beginning 30 minutes after ingestion and continuing for approximately four hours, except that a noted increase in motor activity lasted several more hours. Shulgin concluded that the "psychopharmacological profiles of MDA and MDMA are very similar. (GG-5, A-A4)

47. The Haight-Ashbury Free Medical Clinic in San Francisco treats approximately 3 to 4 clients per month who seek help for problems arising from the use of MDMA, MMDA or MDA. Individuals seen at the clinic have taken up to 15 doses of MDMA in one day, likely to be 50 to 150mg. each. The use of higher doses produces rapid pulse and heartbeat, severe anxiety, paranoia, fear, insomnia, psychological craving for the drug and depression. (Inaba, direct, p. 2; Seymour, direct, p. 3)

48. Dr. Siegel in his interviews with 171 individuals who claim to have used MDMA in the Los Angeles, California area, reports that

effects of MDMA at low doses approximate those of low doses of mescaline, and that effects reported for higher doses of MDMA (200mg.) produce effects similar to those of LSD. (Siegel, direct, p. 3) The high dose effects include hallucinations, either visual, tactile, olfactory or auditory. (Siegel, T-8, p. 46, 49, 50)

49. Low to moderate doses of MDMA have been given to individuals by psychiatrists. Some of these psychiatrists claimed that the MDMA administered was made by them under the supervision of Dr. Shulgin in his laboratory in California. (Greer, T-3, p. 10, 11; Wolfson, T-2, p. 37, 38, 39; Ingrasci, T-7, p. 31)

50. MDMA has been reported, by the psychiatrists administering to themselves and others, and by other individuals to produce the following physical effects: jaw clenching, anorexia, insomnia, flight of ideas, increased heart and pulse rate, mydriasis, nystagmus, blurred vision, enhanced deep tendon reflexes, fatigue after use, ataxia, nausea, vomitting, headache and shakiness. (Downing, direct, exhibit 1, p. 3-6; Greer, direct, exhibit 1, p. 4-5; Ingrasci, direct, p. 5; Grinspoon, T-6, p. 77, 79; Lynch, T-2, p. 98, Sapienza, direct, exhibit 6, p. 3; Vaupel, direct, exhibits 2 and 3)

51. Psychological effects reported for low to moderate doses of MDMA include euphoria, sense of well-being, increases in physical and emotional energy, focus on the here and now, impaired judgement, heightened sensual awareness, anxiety, brief short term memory loss, distortion in depth perception, brief hallucination, visual illusion, nervousness, mild depression, mental fatigue, confusion and altered

state of consciousness. (Downing, direct, p. 3; Downing, direct, exhibit, p. 4-5; Greer, direct, exhibit, pp. 4-5; Ingrasci, direct, p. 5; Wolfson, T-2, p. 48; Lynch, T-2, p. 96; Grinspoon, T-6, p. 80)

52. MDMA was first identified by a DEA laboratory in 1972. Between 1972 and April, 1985, DEA laboratories have identified 41 exhibits of MDMA consisting of over 60,000 dosage units. (Sapienza, direct, pp. 6-8; A-B2)

53. Since its temporary placement into Schedule I on July 1, 1985, MDMA has been identified in at least 14 exhibits submitted to DEA laboratories from Texas alone. These 14 exhibits contained over 35,000 dosage units of MDMA. (Sapienza, T-5, p. 62)

54. MDMA is available in tablets, capsules and powders with recent analyses indicating approximately 110mg. of racemic MDMA per dosage unit. MDMA has been encountered in many sections of the United States and other countries. (Sapienza, direct, p. 6, 8, 9, 10, 11; Chester, direct, p. 3)

55. Since 1978, nonfederal forensic laboratories have reported at least 50 exhibits of MDMA to DEA. (Sapienza, direct, p. 6-8; A-B2; A-B11(a-l))

56. Pharm Chem Laboratories and Toxicology Testing Service are laboratories which provide confidential analysis of drug samples voluntarily submitted to them. Their data provides information on the availability of street drugs and trends in drug abuse patterns. (A-B16, A-B17)

57. Between 1973 and 1983, Pharm Chem Laboratories reported MDA and MDMA in the same category. The total number of submissions of

MDA/MDMA between 1973 and 1983 was 610, ranging from 21 in 1974 to 88 in 1978. (A-B16, p. 2)

58. Pharm Chem reported 20 submissions of MDMA between May, 1983 and May, 1984 when it discontinued its testing service. (Sapienza, direct, p. 10)

59. Toxicology Testing Service reported 19 submissions of MDMA between April, 1984 and March, 1985. (A-B17)

60. In its investigation of the clandestine manufacture of controlled substances, DEA has encountered five laboratories producing or possessing the necessary chemicals to produce MDMA. Each laboratory had produced or had the capability of producing kilogram (10,000 dosage units) quantities of MDMA. Impurities found in the MDMA analyzed by forensic laboratories indicate that MDMA is produced in clandestine laboratories. (Sapienza, direct, pp. 7-8; A-B2)

61. A DEA investigation conducted in June, 1984, of a suspected cocaine distributor resulted in information concerning the wide-spread availability of "Ecstacy" or MDMA in the Dallas, Texas area. (Chester, direct, p. 1)

62. "Ecstacy" or MDMA, with a claimed origination of California, was being distributed in the Dallas area in 100 tablet bottles by organized groups. The tablets were found to contain approximately 110mg. of MDMA. (Chester, direct, p. 3)

63. Street prices for MDMA in 1985 were found to be $750 for 1,000 doses in Austin, Texas; $12.50 per dose in Boulder, Colorado; (Sapienza, direct, exhibit 8) $70 per gram in New York, $85 per gram

in Calfornia, and $10-20 per dose in New Hampshire. (A-B17)

64. Dr. Inaba from the Haight-Asbury Clinic in San Francisco reports medically unsupervised use of MDMA in San Francisco by the gay male population, young professionals and individuals with a history of hallucinogenic drug use. (Inaba, direct, p. 2-3)

65. Dr. Siegel of UCLA estimates that the street distribution of MDMA has risen from 10,000 dosage units in 1976 to 30,000 dosage units per month in 1985. (Siegel, direct, p. 2-3, T-8, p. 54-55)

66. Students at the University of Texas in Austin indicate that MDMA is easily available on campus at about $5 to $20 a tablet. (A-C1)

67. Dr. Ingrasci has interviewed over 500 individuals who have used MDMA over the past seven to eight years. More than half of these individuals had used MDMA in a non-therapeutically motivated setting for curiosity or recreation. (Ingrasci, direct, p. 1, T-7, p. 38-39)

68. The 22 subjects in Dr. Downing's MDMA study admitted to previous use of MDMA. One had used MDMA 12 times, one 10 times, with the mean frequency of use being once every 2.2 months. (Downing, direct, attachment 3, p. 1, 2)

69. Dr. Grinspoon reports that MDMA is being taken by a growing number of people, particularly students and young professionals in a casual and recreational manner. (Grinspoon, direct, p. 4-5)

70. An individual described by Dr. Greer who had taken 350mg. of MDMA reported visual hallucinations, illusions, hearing impairment, brief memory loss and distortion in depth perception. (Greer, direct,

exhibit, p. 4)

71. Between 1977 and 1981, the Drug Abuse Warning Network (DAWN) reported eight emergency room episodes associated with the use of MDMA. (A-B2, attachment 5)

72. MDMA is known to have been associated with two overdose deaths. One death occurred in Seattle, Washington in 1979, and one in Santa Monica, California. (A-B2, A-B15, A-B18, A-B19)

73. The Assistant Secretary of Health, Department of Health and Human Services, in his scientific and medical evaluation of MDMA concluded that MDMA has a high potential for abuse. (A-B3, A-B4)

Discussion

The available scientific data clearly show that MDMA produces physical and psychological effects in common with central nervous system stimulants like amphetamine, and with known hallucinogens or psychotomimetics like MDA in both animals and humans. The chemical structure of MDMA is very closely related to MDA and to methamphetamine. Its pharmacological properties are almost identical to those of MDA. In preliminary studies MDMA has been shown to be neurotoxic in animals, just as MDA has been shown to be neurotoxic. In the studies conducted specifically to determine abuse liability, MDMA has been shown to have an abuse liability similar to stimulants such as cocaine and amphetamine. MDMA is a substance which is clandestinely produced and trafficked on the street in the United States, and is taken for its pleasurable effects.

Animal and human studies which completely characterize the pharmacology, safety and efficacy of MDMA are not available.

Although the research being conducted on MDMA is increasing, there are still many unanswered questions. More information is always helpful, but as Congress indicated in the legislative history of the scheduling provisions of the Controlled Substances Act, "the Secretary of Health, Education, and Welfare should not be required to wait until a number of lives have been destroyed or substantial problems have already arisen before designating a drug as subject to the controls of this bill." 30/

MDMA is stucturally similar to MDA, amphetamine and methamphetamine. Changes in the chemical structure of any substance may result in changes in the quantitative and/or qualitative effects produced. Regarding MDA and MDMA these changes are described as subtle and are more a function of the amount taken. MDMA retains the structural features of MDA which are consistent with the production of stimulant and hallucinogenic effects. Other compounds which have methylendioxy and or methoxy substituents on the aromatic nucleus of amphetamine include para-methoxy-amphetamine (PMA), 3,4,5-trimethoxy-amphetamine (TMA), 4-methyl-2,5-dimethoxyamphetamine (STP, DOM), 2,5-dimethoxyamphetamine (DMA), 3-methoxy-4,5-methylenedioxy-amphetamine (MMDA) and the previously mentioned 3,4-methlenedioxyamphetamine (MDA). All are listed as hallucinogens in Schedule I of the Controlled Substances Act. 31/

30/ [1970] U.S. Code Cong. & Admin. News 4602

31/ 21 U.S.C. § 812(c)I(c)

Different species of animals: mice, rats, rabbits, monkeys, dogs and baboons have been given MDMA in certain testing situations. They exhibited the increased locomotor activity and stimulation characteristic of central nervous system stimulants like amphetamine. Toxicity studies showed that MDA and MDMA exhibit the amphetamine-like property of increased lethality under aggregated housing conditions. Mice, dogs and monkeys have been observed as excitable, aggressive, and experiencing hallucinations after having taken high doses of MDMA. Rabbits show an increase in body temperature when administered MDMA, another characteristic of centrally acting compounds.

The lethal dose of MDMA as determined in toxicology studies shows it to be more lethal than the Schedule I hallucinogen mescaline, but somewhat less lethal than MDA. In mice MDMA was found to be more lethal than d-amphetamine. MDA, MDMA, amphetamine and methamphetamine have been shown to be neurotoxic in animals. They have been found to destroy the brain cells which utilize the substance serotonin. These cells are associated with mood, emotion, pain perception, and sleep. MDA and MDMA have shown a much higher neurotoxicity to the serotonergic brain cells than amphetamine and methamphetamine. The studies have shown that even a single dose of MDA or MDMA causes neurotoxic damage. Although these types of studies cannot be conducted on humans, MDMA and MDA are likely to produce the same neurotoxic effects to serotoneric nerve cells in humans at doese which are being used by MDMA abusers.

Abuse liability of a substance is a term used to refer to the

likelihood that a substance will be abused and the untoward effects of abusing a substance. The untoward effects of substance abuse include its physical and psychological dependence. Although many compounds which are abused do not cause physical dependence, they do have reinforcing qualities which cause animals and humans to seek their use. Two types of procedures are commonly employed in determining the abuse liability of a substance in animals. They are drug discrimination paradigms and drug self-administration paradigms. The techniques utilized in these types of studies are especially useful with drugs that act on the central nervous system. 32/

Drug discrimination studies which have been conducted with MDA and MDMA show that animals trained to discriminate between amphetamine and saline recognize both MDA and MDMA as like amphetamine and not like saline. Animals trained to recognize MDA also recognize MDMA. In self-administration studies with monkeys and baboons MDMA was substituted for cocaine. The monkeys and baboons had been trained to work in order to get a dose of cocaine. When MDMA was substituted for the cocaine, the animals continued to work in order to obtain the MDMA. These animals therefore recognize effects from MDMA similar to those they experienced from amphetamine and cocaine. Humans also recognize these effects.

MDMA has not been the subject of any scientifically controlled clinical studies in humans. Humans have however, been observed while taking MDMA, and during this proceeding several witnesses described their own recollection of the effects of self-administered MDMA. All

32/"Testing Drugs for Physical Dependence Potential and Abuse Liability," NIDA Research Monograph 52, 1984.

reports of human ingestion of MDMA contain common threads. There were physical symptoms of increased heart rate and pulse after taking the MDMA, and fatigue after several hours. Jaw clenching was a commonly reported physical symptom. Various psychological effects described as intoxication, euphoria, sense of well-being, and altered states of consciousness have been reported at doses of approximately 100mg. Dr. Downing described himself as lying in a "twilight state" during his MDMA experience, and one of his patients described her experience as:

> In taking the MDMA, I took 150mg. initially, then took a 50mg. booster 2 to 3 hours later. I moved in and out of the attack [recounting a rape] . . .being plunged into the horror, then I would move into a transitional phase of repression. . . I was not consciously aware of this phase. My experience seemed to alternate between these two phases, and at times I would "come around" with what was reported as an exceptional presence. . .a vibrance, color change. . . an expansive quality. . . with a beaming sort of aura. 33/

These descriptions parallel those of other individuals who have taken MDMA and other hallucinogenic amphetamines.

In addition to the reports of those physicians who took MDMA and administered it to their patients, there are numerous indicators that individuals are seeking and taking MDMA outside any therapeutically related setting. The Haight-Asbury Free Medical Clinic in San Francisco, California has been treating individuals who say they have taken MDMA or "Adam" or "Ecstacy" for many years. Dr. Inaba of this clinic claims that he sees the "tip of the iceberg" in drug taking situations. Dr. Siegel from Los Angeles interviewed well over 100

33/ Downing, direct, pp. 12-13

individuals who had taken MDMA. Drs. Inaba and Siegel, who are well-acquainted with drug abusers and the effects of drugs of abuse, indicate that MDMA produces the same effects as MDA and hallucinogenic amphetamines. Anonymous sample testing laboratories in California and Florida have identified MDMA in numerous samples submitted for analysis. DEA has identified five clandestine laboratories either manufacturing or prepared to manufacture MDMA. Law enforcement agencies have been purchasing or seizing significant quantities of MDMA which have gone to their laboratories for analysis. Since the substance has become controlled on a temporary basis the submissions to the DEA laboratories have dramatically increased lending credibility to the statement that uncontrolled substances are not sought out by law enforcement agencies and therefore the laboratory submissions of uncontrolled substances are lower than street availability would indicate.

There is direct evidence in Texas that MDMA is being trafficked by organized groups in much the same manner as known drugs of abuse such as cocaine. Tablets of MDMA, clandestinely manufactured since there is no pharmaceutical manufacturer, are selling nationwide for about $20 a tablet. MDMA is also available in capsules and powder. It is trafficked under the names Ecstacy, XTC and Adam.

The health hazards associated with the use of MDMA are similar to and likely to be of the same degree as those associated with the use of MDA and other hallucinogenic amphetamines. Individuals have sought emergency medical care and treatment for MDMA related problems. Users have taken multiple doses of MDMA and are seeking

treatment for the same problems associated with use of MDA and other hallucinogenic amphetamines. Although many of the problems associated with MDMA use are psychological in nature, there have been two deaths related to the use of MDMA. Those who claim that MDMA is a drug free of serious adverse side effects admit that MDMA could produce serious consequences and different experiences when used in a medically unsupervised setting at higher doses than given "therapeutically." MDMA is taken in multiple doses. It causes impaired functioning. It is likely to produce long term neurotoxic effects in humans. The use of MDMA constitutes a serious hazard to the public health and safety.

MDMA exhibits properties of both stimulants and hallucinogens. The physical and psychological effects observed in humans and in animals are the very ones listed in the previously provided definitions of stimulant and hallucinogen. MDMA is remarkably similar to MDA, a Schedule I controlled substance, and amphetamine and methamphetamine, Schedule II controlled substances with high potentials for abuse. MDMA is a drug sought after and widely available in the illicit traffic. It is produced in clandestine laboratories specifically for abuse purposes. Individuals are abusing it and seeking treatment. MDMA is a relatively untested substance; there are indications that it may be a killer of brain cells associated with emotion, mood and sleep in humans. An untested potentially neurotoxic substance is indeed a risk to the public health.

Conclusions of Law

MDMA has a high potential for abuse. It has a similar chemical structure and pharmacological properties nearly identical to substances already found to have a high potential for abuse. It is clandestinely manufactured, trafficked, and actually abused. Its lack of established safety and potential neurotoxicity make it a serious risk to the public health and safety.

OTHER MATTERS

In addition to the seven issues which have been discussed in this document, there are two other matters which were addressed during the course of these proceedings. These were the effects of international scheduling under the Convention on Psychotropic Substances on domestic scheduling under the Controlled Substances Act, and vice versa, and the impact on research of placing a substance in Schedule I of the Controlled Substances Act. The agency was, and is of the opinion that the effect of control upon research is not a proper subject for consideration in this proceeding. Evidence concerning the subject was received by the Administrative Law Judge over agency objection. Accordingly, we will address this subject briefly in this document. Likewise, the impact of international scheduling and the status of MDMA under the treaty will be discussed.

EFFECTS OF SCHEDULE I CONTROL

Although not properly a finding to be made by the Administrator

in a scheduling proceeding pursuant to 21 U.S.C. § 812(b), nor a factor which is to be addressed when making such findings pursuant to 21 U.S.C. § 811(c), the Administrative Law Judge has deemed the effects upon research of placement in Schedule I to be a matter to be addressed in this proceeding. The agency reiterates its position that this is not a matter relevant to whether a substance should be placed in Schedule I of the Controlled Substances Act.

The Controlled Substances Act contains specific provisions for research with Schedule I substances. These involve specific registration and recordkeeping requirements. The registration provisions are found in 21 U.S.C. § 823(f) and state:

> Registration applications by practitioners wishing to conduct research with controlled substances in schedule I shall be referred to the Secretary, who shall determine qualifications and competency of each practitioner requesting registration, as well as the merits of the research protocol. The Secretary, in determining the merits of each research protocol shall consult with the Attorney General as to effective procedures to adequately safeguard against diversion of such controlled substances from legitimate medical or scientific use. Registration for the purpose of bona fide research with controlled substances in schedule I by a practitioner deemed qualified by the Secretary may be denied by the Attorney General only on a ground specified in section 824(a) of this title.

The information required to be contained in a research protocol is outlined with specificity in 21 CFR § 1301.33. The protocol requirements also make reference to the investigational new drug (IND) procedures. They provide that researchers wishing to conduct clinical (human) investigations with controlled substances in Schedule I must submit three copies of a Notice of Claimed Investigational Exemption for a New Drug (IND) and their security

provisions with their application for registration. This is in lieu of submission of a research protocol.

Section 827 of Title 21, United States Code, outlines the recordkeeping and reporting requirements for all registrants. Paragraph (a) of that section provides that the general recordkeeping requirements shall not apply :

> to the use of controlled substances, at establishments registered under this subchapter which keep records with respect to such substances, in research conducted in conformity with an exemption granted under section 355(i) or 360(j) of this title; 34/

Regulations found in 21 CFR § 1304.03(d) further explain that if a registered establishment keeps the records required by the Federal, Food, Drug and Cosmetic Act under sections 505(i) or 512(j), then the individual researcher in that establishment is not also required to keep records. In 21 U.S.C. § 827(f) there are provisions for the promulgation of regulations to the Food, Drug and Cosmetic Act relating to investigational use of drugs which are controlled substances. Section 827(f) provides that such regulations will contain procedures "to insure the security and accountability of controlled substances used in research . . ." These regulations are found at 21 CFR § 312.10 and state:

> If an investigational drug is subject to the Comprehensive Drug Abuse Prevention and Control Act of 1970, records concerning shipment, delivery, receipt, and disposition of the drug which are required to be kept by §§ 312.1(a)(4), (12), and (13) and 312.9(a)(3) shall, upon the request of a properly authorized employee of the Drug Enforcement Administration of the U.S. Department of Justice, approved by the Secretary, be made available by the investigator or sponsor to whom the request is made, for inspection and copying.

34/ 21 U.S.C. § 827(c)(2)(A)

During the course of hearings which were conducted by both the House of Representatives and the Senate prior to the passage of the Comprehensive Drug Abuse Prevention and Control Act of 1970 there was much discussion of the impact of scheduling upon research. An example of the discussions which took place at these hearings is illustrated by the testimony of E. B. Anderson, Vice President of Hoffmann-LaRoche, Inc. before the Senate Subcommittee to Investigate Juvenile Delinquency on September 29, 1969. Mr. Anderson said:

> Section 303(f) of S. 2637 [enacted as 21 U.S.C. § 823(f)] deals with the application by a scientist to conduct research with substances listed on schedule I--those substances which have no accepted medical use, which the Attorney General designates as having no accepted medical use. While the bills require the application to be referred to the Secretary of HEW for advice, it gives the Attorney General final authority to decide whether research shall be permitted.
>
> We believe that these requirements introduce an element of rigidity and practical difficulty which could seriously hamper research.
>
> Under present law such research with human subjects can only be conducted under the supervision of the Food and Drug Administration. Thus these bills require in addition approval by a different Government agency, a procedure which can only make it more difficult to institute such research. 35/

A discussion then occurred between Mr. Anderson and Chairman Dodd and Dr. Burns, Vice-President of Research for Hoffmann-LaRoche, Inc. in which the following occurred:

Chairman Dodd. Approved by the Attorney General--that has only to do with schedule I drugs.

Mr. Anderson. That is correct.

35/Narcotics Legislation: Hearings on S. 1895, S. 2590 and S.2637 Before the Subcomm. to Investigate Juvenile Delinquency of the Senate Comm. on the Judiciary, 91st Cong., 1st Sess. 628 (1969)

Chariman Dodd. Those are the ones for which there is no approved medical use.

Mr. Anderson. I think that Dr. Burns may have a comment to make on this in just a moment, on that very point where we suggest to you that perhaps the two systems can still be combined, even on schedule I drugs.

Dr. Burns. I should point out that any drug that you take into consideration--take into investigation doesn't have an approved medical use. This is part of the investigation of a new drug procedure.

Chairman Dodd. One of the things you must remember is that we are trying to prevent diversion and, you know, this is a law enforcement function. It is something we must be concerned about.

Mr. Anderson. We are suggesting that there may yet be medical, useful purposes found at some future date for even schedule I drugs, and--

Chairman Dodd. We know there has been some considerable amount of diversion from researchers and by persons passing themselves off as researchers. You must know this, too, don't you?

Mr. Anderson. We have had very little experience with it, Senator. 36/

In his testimony before the House Subcommittee on Public Health and Welfare on March 3, 1970, John E. Ingersoll, Director of the Bureau of Narcotics and Dangerous Drugs addressed the concerns expressed by scientists such as Mr. Anderson:

> S. 3246 requires that practitioners wishing to conduct research in Schedule I substances, which are those substances having the highest potential for abuse and no presently accepted medical use, obtain a special registration from the Attorney General. . .
>
> This proviso has been the subject of criticism by some scientists, several of who have testified before this subcommittee. Their primary objection is that they do not wish to have the Attorney General reviewing their research protocols. Rather, they feel this is a function of the Department of Health, Education, and Welfare. However, I want to

36/ Id. 629

> make it clear that the Attorney General's only interest in reviewing these protocols is to ascertain if there are adequate safeguards against diversion and that the physical security of these drugs is insured. He is neither interested in nor qualified to judge what is a good or bad research protocol from a scientific point of view and will not do so. 37/

There was much testimony concerning this issue before several subcommittees. After hearing the arguments Congress passed the Comprehensive Drug Abuse Prevention and Control Act of 1970 with the provisions requiring separate registration for those conducting research in Schedule I. They also required the researcher to submit a protocol which is to be reviewed by the Secretary of Health and Human Services to determine the "qualifications and competency of each practitioner requesting registration." 38/

The records required to be kept by researchers in Schedule I are not substantially different from the records required to be kept by a researcher or dispenser of Schedule II, III, IV, or V controlled substances. In his rebuttal testimony agency witness Larry Snyder outlined the recordkeeping and security requirements for Schedule I researchers and the differences in records required for researchers registered in other schedules:

> Recordkeeping requirements for researchers in Schedule I and II are identical. Recordkeeping requirements for researchers registered to handle controlled substances in Schedules III, IV, and V include biennial inventory, but only an estimated count or measure of each controlled substance is required; records of receipt, but not on DEA triplicate order forms, and complete and accurate records

37/ Drug Abuse Control Amendments: Hearings on H.R. 11701 and H.R. 13743 Before the Subcomm. on Public Health and Welfare of the House Comm. on Interstate and Foreign Commerce, 91st Cong., 2nd Sess. 678 (1970)

38/ 21 U.S.C. § 823(f)

of disposition in the same manner as Schedule I and II researchers. 39/

In comparing the security requirements for researchers in Schedule I as opposed to those in the other schedules, Mr. Snyder stated:

> The security requirements for storage of controlled substances by all researchers are identical, regardless of the Schedule of the substance. All controlled substances must be stored in a securely locked, substantially contructed cabinet. 40/

The major difference in the regulatory requirements imposed upon researchers handling Schedule I controlled substances and those conducting research with Schedule II, III, IV, and V controlled substances is the registration requirements which require review of a protocol by the Secretary of the Department of Health and Human Services. All researchers utilizing controlled substances must be registered by the Drug Enforcement Administration. All researchers must keep records, and all researchers must maintain the controlled substances in a "securely locked, substantially constructed cabinet." 41/

Congress was well aware of the concerns of the pharmaceutical industry and the scientific community concerning the additional registration requirements imposed upon Schedule I researchers. They enacted the legislation which is the Controlled Substances Act after extensive hearings in which these individuals and companies had every opportunity to express their views. Since Congress has already

39/ Snyder, rebuttal testimony, p. 2-3.

40/ Id., p. 3.

41/ 21 C.F.R. § 1301.75

considered the issue of the restrictions imposed by Schedule I control upon researchers, it is not necessary for the Administrator to address the issue in this proceeding.

INTERNATIONAL SCHEDULING

In 1978 Congress amended the Controlled Substances Act by enacting the Psychotropic Substances Act of 1978, Pub. L. 95-633. Congress made as one of its findings and declarations the following statement:

> The United States has joined with other countries in executing an international treaty, entitled the Convention on Psychotropic Substances and signed at Vienna, Austria, on February 21, 1971, which is designed to establish suitable controls over the manufacture, distribution, transfer, and use of certain psychotropic substances. The Convention is not self-executing, and the obligations of the United States thereunder may only be performed pursuant to appropriate legislation. It is the intent of the Congress that the amendments made by this Act, together with existing law, will enable the United States to meet all of its obligations under the Convention and that no further legislation will be necessary for that purpose. 42/

The Psychotropic Substances Act amended portions of 21 U.S.C. § 811(d) to provide for the initiation of scheduling proceedings by the Secretary and the Attorney General after notice of a scheduling decision pursuant to article 2 of the Convention on Psychotropic Substances is received by the Secretary of State. It also provided for publication notice and public hearings and the compilation of information for submission on behalf of the United States to the World Health Organization regarding proposed scheduling actions under

42/ 21 U.S.C. § 801a(2)

the Convention on Psychotropic Substances. 43/

In 1983, the World Health Organization, on its own initiative undertook the review of 30 substances classified as phenethylamines for possible control under the Convention on Psychotropic Substances. One of these 30 substances was (MDMA). 44/

Article 2 of the Convention on Psychotropic Substances provides that the World Health Organization shall examine the data available and collected from the Parties to the Convention and make findings regarding the pharmacology and abuse of the substance and make a recommendation to the Commission on Narcotic Drugs. The findings of the World Health Organization are binding on the Commission as to medical and scientific matters. Article 2 states in part

> the World Health Organization shall communicate to the Commission an assessment of the substance, including the extent or likelihood of abuse, the degree of seriousness of the public health and social problem and the degree of usefulness of the substance in medical therapy, together with control measures, if any, that would be appropriate in light of its assessment. 45/

After receiving information from the Parties to the Convention concerning the phenethylamines, the World Health Organization (WHO) staff prepared a document titled, "Critical Review of Information on 28 Uncontrolled Phenethylamines for the 22nd Expert Committee on Drug Dependence." (A-B5) This document contained all the available information regarding the chemistry, pharmacology, abuse liability,

43/ 21 U.S.C. § 811(a)(2)(A)

44/ 48 Fed. Reg. 41096 (September 13, 1983)

45/ Convention on Psychotropic Substances 1971, 32 U.S.T. 543, T.I.A.S. No. 9725.

therapeutic use, public health problems and illicit trafficking of these phenethylamines. WHO expert committee reviewed all the data and prepared a report in which it recommended 17 phenethylamines for scheduling under the Convention on Psychotropic Substances. Excerpts of this report were submitted by the Secretary-General of the United Nations to the Secretary of State of the United States of America. Seven of the substances were recommended for placement in Schedule I of the Convention. Included in those seven was 3,4-methylenedioxymeth-amphetamine (MDMA). The Committee stated

> MDMA meets the criteria of Article 2, paragraph 4(a) of the Convention, and there is sufficient evidence that the substance is, or is likely to be abused so as to constitute a public health and social problem warranting placing it under international control.
>
> Therefore, the World Health Organization recommends that MDMA be added to Schedule I of the Convention on Psychotropic Substances, 1971. 46/

In discussing its review of MDMA, the expert committee made the following observations:

> It should be noted that the Committee held extensive discussions concerning the reported therapeutic usefulness of MDMA. While the Committee found the reports intriguing, it was felt that the studies lacked the appropriate methodological design necessary to ascertain the reliability of the observations. There was, however, sufficient interest expressed to recommend that investigations be encouraged to follow up these preliminary findings. 47/

Article 7 of the Convention on Psychotropic Substances 1971, lists special provisions for substances in Schedule I. Included in these provisions is the statement that the Parties shall:

46/ A-B20, Annex I, p. 6.

47/ A-B20, Annex II, p. 8.

(a) Prohibit all use except for scientific and very limited medical purposes by duly authorized persons, in medical or scientific establishments which are directly under the control of their Governments or specifically approved by them. 48/

If the Commission adopts the recommendation of the World Health Organization and places MDMA in Schedule I of the Convention, the United States is required by the treaty and by 21 U.S.C. § 811 to make a determination if the existing controls upon MDMA in the United States meet the requirements of the schedule of the Convention into which the substance is placed. If the Secretary and the Attorney General do not feel that the existing controls meet the minimum requirements of the Convention then scheduling action must be initiated in order to comply with the Convention.

If MDMA is placed in Schedule I of the Convention on Psychotropic Substances 1971, the only Controlled Substances Act schedules sufficiently restrictive to comply with the restrictions provided in the Convention would be Schedule I or II.

SUMMARY

During this proceeding many facts, opinions and speculations have been presented about the drug MDMA. The various parties to this proceeding represent many diverse interests. The agency's interest is directed to protecting the health and safety of the public.

MDMA is a drug which has been the subject of limited animal and

48/ Convention on Psychotropic Substances, 1971, 32 U.S.T. 543, T.I.A.S. No. 9725, Article 7, paragraph a.

human testing. It is a drug which on its face may not appear to be a significant hazard to the public. While we know that MDMA is being clandestinely manufactured and trafficked, we have not seen a great number of deaths or immediate injury among those who have taken it. There may be many facts which we do not know about the long term effects of the drug, or the effects of prolonged use. While there are anecdotal reports from humans who have taken MDMA, there is not sufficient animal data available to justify the investigational use of MDMA in humans pursuant to FDA requirements.

The agency is not in opposition to the concerns of Drs. Greer and Grinspoon et al. MDMA does appear to be an interesting compound and may have a place in medical treatment. The agency is not opposed to MDMA research. There has, however, not been sufficient controlled scientific studies of MDMA to allow therapeutic use of MDMA in humans at this time. When such studies are completed and the drug is approved to be marketed by the Food and Drug Administration, an accepted medical use for the drug will be established.

The Food, Drug and Cosmetic Act provides an elaborate and comprehensive system of approval for drugs prior to marketing in the United States. Pharmaceutical companies or sponsors of drugs must submit extensive scientific studies to show that the drug is safe and effective for its intended therapeutic purpose. Exemptions from this approval process are allowed for pre-clinical and clinical testing. This testing must be conducted under certain conditions, and clinical or human testing must be conducted pursuant to an FDA approved protocol. Prior to testing in which human subjects are utilized,

a drug's chemistry, pharmacology in animals, and safety must be established. These statutory requirements under United States law are taken from guidelines for human experimental research established internationally by the Nuremberg Code and the Declaration of Helsinki. These international documents describe the parameters and ethics under which human testing should be conducted. One of the basic principles outlined in the Declaration of Helsinki is

> Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature. 49/

The psychiatrists who testified in this proceeding administered MDMA to individuals outside the scope of the human investigative parameters mandated by the Food, Drug and Cosmetic Act, and the international medical community. They administered a drug to humans with no estabished safety or efficacy. They administered a drug to humans which was not manufactured in a licensed facility pursuant to good manufacturing practices.

While the Drug Enforcement Administration is not the agency responsible for enforcing these various regulatory requirements and international agreements, the Administrator must consider such factors when determining the meaning of "currently accepted medical use in treatment in the United States" and "lack of accepted safety for use . . . under medical supervision." How could a substance which has not been approved to be given to humans in experimental research situations, much less not manufactured or marketed in this

49/ See Appendix 1.

country, have a "currently accepted medical use . . . in treatment?"

The agency has amply demonstrated that the drug 3,4-methylene-dioxymethamphetamine (MDMA) has no "currently accepted medical use in treatment in the United States", that it lacks "accepted safety for use . . . under medical supervision," and that it has a high potential for abuse. The agency respectfully submits that the Administrative Law Judge must conclude that the evidence substantially supports the conclusion that MDMA meets all the criteria for placement in Schedule I. The agency further submits that the Administrative Law Judge must recommend that the Administrator of the Drug Enforcement Administration should make such a finding.

Respectfully submitted,

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Associate Chief Counsel

Charlotte A. Johnson
Attorney
Office of Chief Counsel
Drug Enforcement Administration

Dated: December 10, 1985

CERTIFICATE OF SERVICE

On December 10, 1985, I caused a copy of the foregoing to be mailed, postage prepaid, to the following:

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correction. If the conditions of the exemption are not immediately met, the sponsor shall have an opportunity for a regulatory hearing before the Food and Drug Administration pursuant to Part 16 of this chapter. If the exemption is terminated, the sponsor shall recall or have destroyed the unused supplies of the drug.

[39 FR 11712, Mar. 29, 1974; 41 FR 48266, Nov. 2, 1976, as amended at 42 FR 15674, Mar. 22, 1977]

Subpart B—Controlled Substances

§ 312.10 Availability of records.

If an investigational drug is subject to the Comprehensive Drug Abuse Prevention and Control Act of 1970, records concerning shipment, delivery, receipt, and disposition of the drug, which are required to be kept by §§ 312.1(a)(4), (12), and (13) and 312.9(a)(3) shall, upon the request of a properly authorized employee of the Drug Enforcement Administration of the U.S. Department of Justice, approved by the Secretary, be made available by the investigator or sponsor to whom the request is made, for inspection and copying.

Subpart C—International Research

§ 312.20 Clinical data generated outside the United States and not subject to a "Notice of Claimed Investigational Exemption for a New Drug."

(a) The Food and Drug Administration's access to data produced by drug studies performed outside of the United States and not covered by a "Notice of Claimed Investigational Exemption for a New Drug" (IND) has been limited largely to review of published literature. The Commissioner of Food and Drugs has concluded that it is in the interest of the public health, whenever possible, to have access to and to consider detailed information resulting from those studies performed abroad which are well-conceived, well-controlled, performed by qualified experts, and conducted in accordance with ethical principles acceptable to the world community.

(b) Such studies may be utilized to support clinical investigations in the United States and in support of the safety and effectiveness of a new drug in a new drug application (NDA) or biological product license application provided all the following conditions are met:

(1) For each investigator's studies, the IND sponsor, NDA applicant or biological product license applicant verifies that:

(i) The investigator is well qualified by scientific training and experience to conduct investigational studies of the subject drug and he is affiliated with a recognized medical school or with an independent institution recognized for its excellence or is otherwise appropriately qualified. Documentation of the investigator's qualifications shall be submitted.

(ii) The investigator has adequate facilities appropriate for the complexity of the studies performed.

(iii) The investigator maintains detailed case records and will complete the sponsor's case report forms or provide the sponsor with the data from his records so that the forms can be completed. He shall also make available to the sponsor any additional background data from such records, including hospital or other institutional records, should such background data be requested by the Food and Drug Administration.

(iv) The investigator has conducted the studies in conformance with the "Declaration of Helsinki" or the laws and regulations of the country in which the research is conducted, whichever represents the greater protection of the individual. If the standards of the country are used, differences from those of the "Declaration of Helsinki," which reads as follows, shall be stated in detail.

RECOMMENDATIONS GUIDING MEDICAL DOCTORS IN BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human sub-

jects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Doctors should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Doctors should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the doctor is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The doctor should then obtain the subject's given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the doctor should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a doctor who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (CLINICAL RESEARCH)

1. In the treatment of the sick person, the doctor must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic methods.

4. The refusal of the patient to participate in a study must never interfere with the doctor-patient relationship.

5. If the doctor considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1, 2).

6. The doctor can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (NON-CLINICAL BIOMEDICAL RESEARCH)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers—either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take prece-

dence over considerations related to the well-being of the subject.

(v) An explanation as to how the research conformed to the principles of the declaration is provided, e.g., for nontherapeutic clinical research it should be clear that the nature, purpose and risk of the research was explained to the subject and his consent was obtained.

(vi) If the investigator's study was conducted on institutionalized subjects, or was conducted on non-institutionalized subjects through an institution which assumed responsibility for the study, either the study has been reviewed for scientific and ethical considerations and approved by a review committee prior to initiation of the study, or the study has been conducted in conformance with the laws, regulations, and scientific and ethical standards of clinical research of the country in which the research was conducted. A review committee, as used in this paragraph, means a committee composed of individuals who are scientists and, where practicable, individuals who are otherwise qualified; in this regard, the addition of other health professionals or laymen to the committee is not required but is desirable. The investigator may not vote on any aspect of the review of his protocol by a review committee. Documentation of review and approval by a review committee shall be submitted and shall include the names and qualifications of the members of the committee. (Procedures for the organization and operation of institutional review committees are contained in the Department of Health and Human Services regulations on "Protection of Human Rights," 45 CFR Part 46.) Where review and approval by a review committee have not occurred prior to initiation of the study, the IND sponsor, NDA applicant or biological product license applicant shall describe how the study conformed to the laws, regulations and scientific and ethical standards of clinical research in the country in which the research was conducted (e.g., whether any review mechanism is required by law and whether the study met such review, whether the investigator and facilities meet the scientific standards in the country, whether the investigator was fully informed of the results of animal toxicity and prior human safety studies, and whether patient consent procedures were required and were followed).

(2) The IND sponsor, NDA applicant or biological product license applicant submits a detailed summary of the preclinical and clinical data and a description of the components, composition, and manufacturing procedures as described in Form FD-1571, items 1, 2, 3, 4, and 5 (§ 312.1(a)(2)), to give significance to the preclinical and clinical data submitted and to permit comparison with data obtained from other studies on the drug.

(c) Data from studies performed abroad and conducted in accordance with the requirements of this section may be utilized without duplication of the studies in the United States, as appropriate. For example, data from phase 1 studies may permit beginning phase 2 studies in the United States; data from phase 2 may permit initiation of later and more extensive phase 2 studies in the United States; phase 2 studies may on occasion be unnecessary in the United States, depending upon the magnitude and quality of the studies and the drug under investigation; data from phase 3 studies may be utilized to supplement phase 3 studies performed in the United States. (For definition of phases 1, 2, 3, see Form FD-1571, item 10 (§ 312.1(a) (2).) When studies from abroad have been performed prior to initiation of United States studies under an IND, the sponsor shall arrange a meeting with the appropriate division, Office of Scientific Evaluation, Bureau of Drugs, or with the appropriate division, Bureau of Biologics, following the division's review of the data, to determine what additional studies will be required in the United States. If studies have been essentially completed in the United States and abroad and the data from the latter are to be incorporated as part of an NDA submission, or biological product license application, they should be included at the time of submission of the NDA, or biological product license application, if possible, but may be

DEWEY, BALLANTINE, BUSHBY, PALMER & WOOD

TO Dr. Shulgin

For your information

Rick Cotton

Dec. 12 , 19 85