

UNITED STATES DEPARTMENT OF JUSTICE  
DRUG ENFORCEMENT ADMINISTRATION

IN THE MATTER OF  
MDMA SCHEDULING

)  
) Docket No. 84-48  
)

GOVERNMENT'S RESPONSE TO  
THE FINDINGS OF FACT, CONCLUSIONS OF LAW,  
AND ARGUMENTS SUBMITTED BY  
DRS. GREER AND GRINSPOON, ET AL.,  
LYN B. EHRNSTEIN, AND HOFFMANN-LA ROCHE, INC.

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This memorandum is submitted in response to the Brief, including Proposed Findings of Fact and Conclusions of Law, on behalf of Drs. Greer and Grinspoon, Professors Bakalar and Roberts; the Proposed Findings of Fact and Conclusions of Law with Supporting Statement of Reasons submitted by Lyn B. Ehrnstein; and the Proposed Findings of Fact, Conclusions of Law, and Argument submitted by Hoffmann-La Roche, Inc., which have been filed in this matter.

#### INTRODUCTION

The compelling and predominant issue in this matter is: Should the substance 3,4 methylenedioxymethamphetamine (MDMA) be scheduled under the Controlled Substances Act, and if so, into what schedule should it be placed? The interests of the parties are varied as shown by the Proposed Findings of Fact and Conclusions of Law submitted. Hoffmann-La Roche, Inc. has expressed no interest in the scheduling of MDMA; their express concern is the meaning of the phrase "currently accepted medical use in treatment in the United States." Drs. Greer and Grinspoon, Professors Bakalar and Roberts agree with the agency that MDMA should be scheduled under the Controlled Substances Act, but argue that MDMA should be placed in Schedule III, not Schedule I. Mr. Ehrnstein contends that MDMA cannot be scheduled.

The agency will address three main topics in this Response; the meaning of accepted medical use in treatment in the United States; the adequacy of the scientific and medical findings provided by the Assistant Secretary for Health, Department of Health and Human Services; and the term potential for abuse as it relates to the scheduling of MDMA.

ACCEPTED MEDICAL USE

One of the three findings required to be made by the Attorney General (Administrator of the Drug Enforcement Administration) for placement of a substance in Schedule I of the Controlled Substances Act is:

- (B) The drug or other substance has no currently accepted medical use in treatment in the United States.<sup>1/</sup>

In response to issue number two in this proceeding, "What constitutes 'currently accepted medical use in treatment in the United States' within the purview of 21 U.S.C § 812(b)?" The parties have provided the following positions:

- 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. (Government's Position)
- The term "currently accepted medical use in treatment in the United States" means that the medical and scientific community in the United States, after considering the particular risks and benefits of the drug, the disease condition to be treated, and the drug's potential medical significance, concludes that use of the drug

1/21 U.S.C. § 812(b)

for that purpose constitutes acceptable treatment. "Currently accepted medical use" can be demonstrated by FDA's approval of a new drug application, by clinical testing, by reports in the scientific literature, by the informed judgment of members of the medical community, and by other relevant means. (Hoffmann-La Roche, Inc.'s Position)

- "Accepted medical use in treatment in the United States" means that the use of a particular drug is accepted by reputable physicians. Those physicians need not constitute the majority, but they must be reputable physicians who constitute at least a respectable minority of practitioners within the medical community. (Drs. Greer and Grinspoon, et al.'s Position)
- "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. FDA's approval of a New Application (NDA) establishes this acceptance. (Mr. Joranson's Position) 2/

Drs. Greer and Grinspoon, et al. and Hoffmann-La Roche, Inc., have submitted many arguments in opposition to the Government's definition of "accepted medical use in treatment in the United States." Several of these arguments are related to the concept of an approved new drug application (NDA). The Government's definition does not specify that the drug or other substance has an approved NDA, but that the substance may be lawfully marketed in the United States pursuant to the Federal Food, Drug and Cosmetic Act. One of the ways that a drug may be lawfully marketed is by having an approved NDA. Some substances which do not have an approved NDA are, however,

2/Mr. Ehrnstein provided no position on this issue.

lawfully marketed under the Federal Food, Drug and Cosmetic Act. Examples are grandfathered drugs, those that were on the market prior to the enactment of the Federal Food, Drug and Cosmetic Act in 1938, and approved over-the-counter drugs.

The investigational new drug (IND) process is an exemption to the requirement that a new drug cannot be shipped interstate without an approved NDA. The IND process is provided by statute, 21 U.S.C. § 355(i), specifically to allow for investigational research. Although substances in an IND status cannot be lawfully marketed, they can be used in specific approved circumstances for treatment, instead of just research, for "compassionate" purposes.<sup>3/</sup> Such use, authorized on an individual case-by-case basis, can hardly be characterized as "accepted medical use in treatment in the United States." The drug is authorized to be given in a therapeutic setting to a specific patient, under specifically approved conditions in life-threatening situations when all available treatments have failed. It is important to note that the compassionate use of an investigational drug must be approved by FDA and this approval will be given only if and when the safety of the drug has been established to the point where it can be given to man. (T-7, p. 99, Tocus)

Drugs which are required to have an approved NDA prior to marketing in the United States are "new drugs." This term is

3/Tr-7, p. 93-94, Dr. Tocus

specifically defined in the Federal Food, Drug and Cosmetic Act as follows:

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this chapter it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.<sup>4/</sup>

MDMA is a "new drug". It therefore must have an approved NDA in order to be lawfully marketed in the United States. The facts have clearly established that MDMA has neither an approved NDA nor an IND, the exemption from the NDA requirement for research purposes. Further it has not been approved for "compassionate" use nor is it an orphan drug.

Several of the cases cited by Drs. Greer and Grinspoon, et al. and Hoffmann-La Roche, Inc. to support the contention that FDA does not regulate the practice of medicine relate to the unapproved use of drugs approved for marketing by the FDA.

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<sup>4/</sup> 21 U.S.C. §321(p)

In other words, the drugs are being utilized for some purpose not listed in their labeling or package insert. They have, however, been found safe and effective for some therapeutic use and been approved for marketing in the United States.

Using approved drugs for new indications is a valid and useful tool because the drug's safety for human use has already been determined, as well as its usefulness for some type of treatment. In the case of an unapproved drug, there is no established track record of safety and efficacy under any circumstances. The distinction between unapproved use of an approved drug and use of an unapproved drug is a very important one which is not made by Drs. Greer and Grinspoon, et al. and Hoffmann-La Roche, Inc. in their arguments. Whether it is permissible for physicians to use approved drugs for unapproved uses is not at all relevant to the issues being discussed in this proceeding. Neither the safety nor efficacy of MDMA has been established under any circumstances for any conditions. Indeed, the courts have held that FDA cannot interfere with such activity since that would be regulating the practice of medicine, a power left to the various states. FDA itself has repeatedly acknowledged that it cannot interfere with an individual physician's practice of medicine. Such statements, and the court opinions, have been directed to the unapproved use of approved drugs. As the U.S. Court of Appeals for the Fifth Circuit recognized in citing from a Notice of Proposed

Rulemaking published by FDA in the Federal Register:

Once [an approved] new drug is in a local pharmacy after interstate shipment, the physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the Food and Drug Administration.

This interpretation of the Act is consistent with Congressional intent as indicated in the legislative history of the 1938 Act and the drug amendments of 1962. Throughout the debate leading to the enactment, there were repeated statements that Congress did not intend the Food and Drug Administration to interfere with medical practice and references to the understanding that the bill did not purport to regulate the practice of medicine as between the physician and the patient. Congress recognized a patient's right to seek civil damages in the courts if there should be evidence of malpractice, and declined to provide any legislative restrictions upon the medical profession.<sup>5/</sup>

The court continues by saying:

Of course, while the act was not intended to regulate the practice of medicine, it was obviously intended to control the availability of drugs for prescribing by physicians.<sup>6/</sup>

The issue in the matter before us is what constitutes "accepted medical use in treatment in the United States." Drugs or other substances which do not have an "accepted medical use" under the definition proposed by the agency are unapproved drugs. These are drugs or other substances which have not been found safe and effective by the FDA for any use.

<sup>5/</sup> 37 Fed. Reg. 16503 (1972) cited in United States v. Evers, 643 F. 2d 1043, 1048 (1981)

<sup>6/</sup> Id., p. 1048.

The federal case law regarding distribution and use of unapproved drugs is somewhat limited. The majority of it relates to the use of Laetrile, a substance used by a handful of physicians to treat terminally ill cancer patients. In United States v. Rutherford citizens brought a suit to enjoin the Government from interfering with interstate shipment and sale of Laetrile. Laetrile is a new drug not approved for marketing under the Federal Food, Drug and Cosmetic Act. In deciding that Laetrile was subject to the standards required for approval of a new drug, the Supreme Court found that:

To accept the proposition that the safety and efficacy standards of the Act have no relevance for terminal patients is to deny the Commissioner's authority over all drugs, however toxic or ineffectual for such individuals.<sup>7/</sup>

The court went on to make a comparison which is relevant to the substance at issue here:

If history is any guide, this new market would not be long overlooked. Since the turn of the century, resourceful entrepreneurs have advertised a wide variety of purportedly simple and painless cures for cancer, including liniments of turpentine, mustard oil, eggs, and ammonia; peat moss; arrangements of colored floodlamps; pastes made from glycerin and limburger cheese; mineral tablets; and "Fountain of Youth" mixtures of spices, oil, and suet. In citing these examples, we do not, of course, intend to deprecate the sincerity of Laetrile's current proponents, or to imply any opinion on whether that drug may ultimately prove safe and effective for cancer treatment. But this historical experience does suggest why Congress could reasonably have determined to protect the terminally ill, no less

<sup>7/</sup>United States v. Rutherford, 442 U.S. 543, 557-558.

than other patients, from the vast range of self-styled panaceas that inventive minds can devise.<sup>8/</sup>

Could Congress have less intended to protect psychiatric patients from a substance such as MDMA? While there is no allegation that MDMA might not be a potentially useful drug, it has yet to be found by scientific testing and reliable evidence to be safe and effective.

The Court in Rutherford, in accord with the agency in this proceeding, noted that the Federal Food, Drug and Cosmetic Act has provided an avenue for use of experimental drugs through the exemption process of 21 U.S.C. § 355(i). This is the investigational new drug (IND) process. The court states "...the Act makes explicit provision for carefully regulated use of certain drugs not yet demonstrated safe and effective..."<sup>9/</sup>

Drs. Greer and Grinspoon, et al. also argue that states, especially California, allow physicians to use unapproved drugs in treatment provided they meet certain standards enumerated by state licensing boards, and that such intrastate use of unapproved drugs is outside the purview of the Food and Drug Administration since FDA regulates interstate marketing. The matter at issue is "accepted medical use in treatment in the United States." The standard applies to all fifty states, not just California. Whereas the Federal Food, Drug and Cosmetic

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8/Id., p. 558

9/Id., p. 559

Act, which was passed in 1938, requires a showing of actual interstate transit for many of its offenses, the Controlled Substances Act operates under a presumption of interstate commerce. This is found in 21 U.S.C. § 801, Congressional findings and declarations. Specifically in paragraph (5) Congress found,

(5) controlled substances manufactured and distributed intrastate cannot be differentiated from controlled substances manufactured and distributed interstate. Thus, it is not feasible to distinguish in terms of controls, between controlled substances manufactured and distributed interstate and controlled substances manufactured and distributed intrastate.

In order to establish uniform control of a substance across all fifty states, a finding of "accepted medical use in treatment in the United States" must be applicable across all state boundaries. It is therefore not relevant that California may allow physicians to use unapproved substances in treatment under certain conditions.

The standard which must be applied is a national standard. The use of the Federal Food, Drug and Cosmetic Act to establish this standard is a logical choice. The Food and Drug Administration determines safety and efficacy of substances by an approval process. Once approved, these substances are available to the individual physician. A drug established as safe and effective and made available to the medical community for use in whatever manner they deem acceptable in their professional judgment and subject to their own licensing and

state regulatory restrictions, is a drug with an "accepted medical use in treatment in the United States."

Hoffmann-La Roche, Inc.'s reliance on National Organization for Reform of Marihuana Laws (NORML) v. Drug Enforcement Administration, 559 F.2d 735 (D.C. Cir. 1977) to indicate that the court determined that "accepted medical use in treatment in the United States" cannot be determined on the basis of whether a drug has an approved NDA is a misinterpretation of the case. The Court found that a letter from the Acting Assistant Secretary for Health that stated that marijuana had no currently accepted medical use in the United States did not provide a sufficient explanation for its conclusions that lack of an approved NDA meant that marijuana had no "accepted medical use" in light of the extensive use of marijuana in cancer research. The court held that in the process of securing the letter, the agency did not comply with the procedures required by the statute. In essence, the Court said that it was necessary to elaborate on the statement of the Assistant Secretary for Health and remanded the case for further findings.<sup>10/</sup> The Court never reached the issue of whether lack of an approved NDA established lack of accepted medical use.

Drs. Greer and Grinspoon, et al. extensively discuss the somewhat sparse legislative history of the Controlled

10/559 F.2d 735, 750

Substances Act relating to "accepted medical use." What is clear from this discussion is that those who testified before the various Congressional committees were not clear or consistent concerning the meaning of the phrase "accepted medical use in treatment in the United States." The phrase "accepted medical use in treatment in the United States" was never explained or clarified in any of the committee reports. It was not a matter of great concern during the hearings on the bill which became the Controlled Substances Act. The testimony of Dr. Jennings, Acting Director of the Bureau of Drugs, Food and Drug Administration, before the House of Representatives Subcommittee on Public Health and Welfare, which was referenced by the Government in their proposed findings of fact, conclusions of law and argument and by Drs. Greer and Grinspoon, et al. in their proposed findings, supports the agency's definition of "accepted medical use in treatment in the United States." Dr. Jennings responded to a question concerning whether a drug under investigation pursuant to an IND had an accepted medical use. He indicated that it would "usually not, although it might." When qualifying this answer, he stated that "However, drugs that have one or maybe several medical uses might be under investigation for additional medical uses." This means that a drug with an approved NDA may be under investigation for additional, currently unapproved uses. This is another example of

unapproved use of approved drugs. In this case, the sponsor of the drug is conducting investigational studies to establish to FDA another approved therapeutic use for the drug. The drug in question, however, does have an approved use and therefore an "accepted medical use."

Since the Department of Health and Human Services, and the Food and Drug Administration, as part of that Department, make the scientific and medical findings required by 21 U.S.C. § 811, their interpretation to Congress of the meaning of "accepted medical use" is especially significant. Dr. Jennings was speaking as a representative of that Department. An additional item of note found in the legislative history of the Controlled Substances Act reinforces Dr. Jennings statement. A physician-researcher, Dr. Jonathan Cole, Chairman, Committee for Effective Drug Abuse Legislation, and in behalf of The American College of Neuro-Psycho Pharmacology testified before the House of Representatives, Committee on Interstate and Foreign Commerce, Subcommittee on Public Health and Welfare on February 18, 1970. He expressed concern about the proposed placement in Schedule I of the substance alphacetylmethadol because it might be potentially useful in treating narcotic addicts. He stated:

There is also the problem of new drug development and as I read the bill, if a company were to make a new tranquilizer and have it begin to be studied in man, and there was a little evidence that it resembled the barbiturates or amphetamine, it would come under control under this act, and would go in schedule I. There are

already a whole set of stringent controls under the Food and Drug Administration, for investigation of new drugs, a good deal of recordkeeping and reporting and other things. If the investigators also had to get a special registration from the Department of Justice, in addition to going through all the Food and Drug Administration paperwork, I think it would discourage drug development substantially, and add a second burden on top of an already possibly somewhat over-controlled area under the new drug act.<sup>11/</sup>

Dr. Cole made the same argument before the Congressional committee which Drs. Greer and Grinspoon, et al. and Hoffmann-La Roche, Inc. are making in this proceeding: that placing a substance which is being researched into Schedule I will discourage further research and development of that substance.

The Bureau of Narcotics and Dangerous Drugs later submitted for the record a "Justification for Placement of Alphacetylmethadol in Schedule I of the Controlled Dangerous Substances Act, S. 3246." In this justification was the statement:

Further, since the current use of alphacetylmethadol is limited to research, it has no currently accepted medical use - that is, no IND or NDA has been issued for it by the Food and Drug Administration.<sup>12/</sup>

Alphacetylmethadol was in Schedule I when the Controlled Substances Act was passed by Congress.<sup>13/</sup>

<sup>11/</sup>Drug Abuse Control Amendments - 1970: Hearings on H.R. 11701 and H.R. 13743 Before the Subcommittee of Public Health and Welfare of the House Committee on Interstate and Foreign Commerce, 91st Cong., 2d Sess. (1970) (Statement of Dr. Jonathan O. Cole, p. 313.)

<sup>12/</sup>Id. (Statement of John E. Ingersoll, Director, Bureau of Narcotics and Dangerous Drugs), p. 715.

<sup>13/</sup>21 U.S.C. § 812, Schedule I(a)(3).

Obviously, Congress was not convinced by Dr. Cole's argument. Even though alphacetylmethadol had been used experimentally to treat heroin addiction, and even though it appeared that the substance had a potential for therapeutic use, Congress chose to place it in Schedule I. The same analogy can be made to LSD. Dr. Grinspoon testified during these proceedings that,

Between 1950 and the mid 1960's there was a robust interest in the possibility that LSD . . . might be therapeutically useful for psychiatry. There were more than a thousand clinical papers discussing forty thousand patients . . . the subject aroused the interest of many psychiatrists. The use of LSD was recommended for a wide variety of problems including alcoholism, obsessional neurosis, and the treatment of the dying. (Grinspoon, direct, p. 1)

Even though MDMA may have a potential therapeutic use, because it lacks a "currently accepted medical use in treatment in the United States", it properly belongs in Schedule I. Since 1970, there is no indication that Congress has changed its position that substances undergoing research which lack an approved NDA and have a potential for abuse belong in any Schedule other than Schedule I.

Even utilizing the definitions of "accepted medical use in treatment in the United States" proposed by Drs. Greer and Grinspoon, et al. and Hoffmann-La Roche, Inc., MDMA would not have an "accepted medical use in treatment in the United States." The evidence in the record indicates that MDMA has been used by only a handful of physicians in a "therapeutic" setting. These physicians, by their own admission, are not

researchers. Dr. Kleinman indicated that these physicians "lack any serious academic or scientific standing in the psychiatric community."<sup>14/</sup> There have been no published clinical studies involving MDMA. Only recently are animal research studies involving MDMA being conducted. There is insufficient scientific data available about MDMA to establish its safety.<sup>15/</sup> The physicians who utilized MDMA in therapy themselves concluded a pilot study by saying, "there is insufficient evidence to judge accurately either harm or benefit."<sup>16/</sup> Two reputable and credentialed psychiatrists testified that they would not utilize an unapproved, untested drug in their practice, and that they would not use MDMA.<sup>17/</sup> MDMA has not been shown to be accepted by a "respectable minority of practitioners within the medical community." MDMA has no approved NDA or IND, it is not an orphan drug, it has not been approved for compassionate uses, it has been the subject of limited, uncontrolled, clinical testing, it has been the subject of few studies reported in the scientific literature, and there is no evidence that it has been "accepted" by the medical community. MDMA has no currently

<sup>14/</sup>Kleinman, direct, p. 2

<sup>15/</sup>Tocus, direct, p. 9

<sup>16/</sup>GG-8

<sup>17/</sup>Tr-5, p. 207-209 (Kleinman); Tr-7, p. 142 (Docherty)

accepted medical use in treatment in the United States by any definition of "accepted medical use in treatment in the United States."

ADEQUACY OF HHS SCIENTIFIC  
AND MEDICAL FINDINGS

The statutory procedure for the scheduling of substances under the Controlled Substances Act is found in 21 U.S.C.

§ 811. Paragraph (b) of that section provides:

(b) The Attorney General shall, before initiating proceedings under subsection (a) of this section to control a drug or other substance or to remove a drug or other substance entirely from the schedules, and after gathering the necessary data request from the Secretary a scientific and medical evaluation, and his recommendations, as to whether such drug or other substance should be so controlled or removed as a controlled substance. In making such evaluation and recommendations, the Secretary shall consider the factors listed in paragraphs (2), (3), (6), (7) and (8) of subsection (c) of this section and any scientific and medical considerations involved in paragraphs (1), (4) and (5) of such subsection ...

Mr. Ehrnstein contends in his Proposed Findings of Fact and Conclusions of Law with Supporting Statement of Reasons that the findings submitted by the Secretary to the Drug Enforcement Administration failed to meet the statutory requirement of Section 811(b). Drs. Greer and Grinspoon, et al. argue that the recommendation of the Secretary is not binding on the Attorney General (Administrator) since the original determination by the Secretary was (1) not in accordance with the law; (2) was arbitrary and capricious; and (3) was not complete because the Secretary did not consider all relevant scientific and medical evidence.

This scheduling process involving MDMA was initiated in March, 1984 by the then-Administrator of the Drug Enforcement Administration. He sent a letter to the Assistant Secretary for Health, Department of Health and Human Services, dated March 13, 1984. This letter requested that the Assistant Secretary provide the Administrator of DEA with a scientific and medical evaluation of MDMA. (A-B1). Enclosed with this letter was a document which had been prepared by the Drug Enforcement Administration entitled: "Schedule I Control Recommendation Under the CSA for 3,4 - methylenedioxymethamphetamine (MDMA)." This document constituted the information compiled by DEA "after gathering necessary data"<sup>18/</sup>, as required by the CSA. The Acting Assistant Secretary for Health forwarded his scientific and medical evaluation with a letter dated June 6, 1984, to the then-Administrator of DEA. (A-B3, B4).

There is no elaboration in the statute of what is required to be provided by the Secretary in his scientific and medical evaluation. Section 811(b) only requires that the evaluation and recommendation be in writing and that the Secretary consider the factors listed in 21 U.S.C. § 811(c). The legislative history provides some explanation on how the Secretary and the Attorney General are to consider the eight factors. After listing each of the eight factors the Report of the Committee on Interstate and Foreign Commerce on the bill 18/21 U.S.C. § 811(b)

that was to become the Controlled Substances Act states:

It should be noted that the abovementioned factors do not require specific findings to be made with respect to control under or removal from, schedules, but rather are factors to be considered in making the special findings required under section 202(b) for control under such schedules. [emphasis added]<sup>19/</sup>

The special findings are the three criteria listed for each schedule which are found in 21 U.S.C. § 812(b).

The statute does not require the Secretary to make an independent medical and scientific evaluation. The concern expressed by Congress in having the Secretary become part of the scheduling process was not that another independent evaluation was necessary, but that the then-Department of Health, Education and Welfare was better equipped to make the scientific and medical evaluation. As part of the Report of the House Committee on Interstate and Foreign Commerce they stated:

The phrase "after gathering necessary data" is not intended to authorize the Attorney General to undertake or support medical and scientific research for that purpose, which is within the competence of the Department of Health, Education and Welfare, or to limit the Secretary's evaluation to data submitted to him by the Attorney General ...<sup>20/</sup>

Here the Committee said that the phrase "after gathering necessary data" did not limit the Secretary's evaluation to data submitted to by the Attorney General. This phrase clearly

<sup>19/</sup>[1970] U.S. Code Cong. and Admin. News 4603.

<sup>20/</sup>Id. 4600.

contemplates that the Attorney General will submit the data collected by him to the Secretary, which was done by the Administrator of DEA in this proceeding. It does not require the Secretary to collect additional data, but allows him to consider additional data which is available. Dr. Tocus of the Food and Drug Administration testified that he sought out additional data through the files of the FDA and the scientific literature, but that he found no other published data.<sup>21/</sup>

Drs. Greer and Grinspoon, et al. present several reasons for their contention that the Secretary's evaluation is invalid. One reason addresses the misapplication of the term "accepted medical use." Since the meaning of this phrase is an issue in this proceeding, there is obviously not an accepted definition of that phrase. The Secretary applied the standard which the Food and Drug Administration has previously published as the Department's standard. This standard was published by the Food and Drug Administration in the Federal Register in 1982.<sup>22/</sup>

Drs. Greer and Grinspoon, et al. argue that the Department of Health and Human Services should have gone outside the agency to obtain information, and utilized one of the many advisory committees available to the Assistant Secretary of Health. Again, there is no requirement that the Secretary go outside the Department to make his evaluation or that the

<sup>21/</sup>Tocus direct, pp. 5-9, Tr-9, pp. 49-50 (Tocus)

<sup>22/47</sup> Fed.Reg. 28141, A-B14

Secretary convene an advisory committee to assist in preparing his scientific and medical evaluation. The purpose of an advisory committee is to assist the Secretary or Assistant Secretary of Health when it is necessary. Public Law 92-463 which lists the standards for formation of these committees states:

Sec. 9. (b) Unless otherwise specifically provided by statute or Presidential directive, advisory committees shall be utilized solely for advisory functions. Determinations of action to be taken and policy to be expressed with respect to matters upon which an advisory committee reports or makes recommendations shall be made solely by the President or an officer of the Federal Government.<sup>23/</sup>

In the case of MDMA, the Assistant Secretary did not feel it was necessary to convene an advisory committee. This is his prerogative. Even if the Assistant Secretary utilizes such committees, he is not required to take their advice or recommendations. Drs. Greer and Grinspoon, et al. contend that the DEA document submitted to the Department of Health and Human Services creates false and misleading impressions regarding the number of MDMA encounters by forensic laboratories. The Secretary is obligated to consider only the factors listed in paragraphs (2), (3), (6), (7), and (8) of 21 U.S.C. § 811(c), and any scientific or medical considerations of paragraphs (1), (4) and (5) of that section. Clearly law enforcement seizure and forensic laboratory data are not

23/[1972] U.S. Code Cong. and Admin. News, p. 897

relevant to factors listed in paragraphs (2), (3), (6), (7), and (8), nor are they scientific and medical considerations under factors (1), (4) and (5). This type of information established that there was MDMA available in the street traffic, but it did not serve as the basis for a scientific and medical evaluation.

In early 1984, the Assistant Secretary of Health, through his delegees, made a scientific and medical evaluation of 3,4 - methylenedioxymethamphetamine (MDMA) based upon data provided by the Drug Enforcement Administration, a review of the scientific literature and the files of the Food and Drug Administration. Consultation with the National Institute on Drug Abuse reinforced the position that there was limited scientific and research data available. A federal agency cannot be expected to be aware of use of a substance by a few physicians who have not published their studies in the recognized scientific literature. A federal agency cannot be expected to retrieve single letters relating to specific drugs from among thousands which they receive from the public. Until there is serious research and a scientific record established, and until some approval process is begun within the Food and Drug Administration, the agency cannot be expected to be aware of isolated use of a non-approved, non-investigation drug. In early 1984, the Food and Drug Administration had no reason to know about possible therapeutic use of MDMA. The Assistant

Secretary of Health provided the Administrator with a scientific and medical evaluation of MDMA in June, 1984. After considering the Assistant Secretary's evaluation and recommendation that MDMA be placed in Schedule I of the Controlled Substance Act, and all the data available at that time, the Administrator proposed that MDMA be placed in Schedule I of the CSA.24/

#### POTENTIAL FOR ABUSE

Included in the Administrator's proposal for placement of MDMA in Schedule I was a finding that MDMA has a high potential for abuse. The evidence presented in the record in this proceeding supports the Administrator's preliminary finding.

Drs. Greer and Grinspoon, et al. argue that MDMA has less than a high potential for abuse and should properly be placed in Schedule III of the Controlled Substances Act based upon its relative potential for abuse. Mr. Ehrnstein argues that MDMA does not have sufficient potential for abuse to be scheduled at all under the Controlled Substances Act.

In their argument, Drs. Greer and Grinspoon, et al. quote substantial portions of the legislative history of the Controlled Substances Act regarding potential for abuse. These sections are indeed important in determining the meaning of "potential for abuse." Indeed, the agency has previously quoted these same passages in this proceeding.

24/49 Fed.Reg. 30210 (July 27, 1984), ALJ-1

One point needs to be emphasized with regard to the language in this portion of the legislative history. The use of the term "diversion" in the quoted portions of the referenced legislative history has a specific and intended meaning.<sup>25/</sup> The term "diversion", as used in these quotations, means distribution outside of or from legitimate channels. This presumes that the drug in question is a marketed pharmaceutical drug and millions of dosage units are in the legitimate distribution chain extending from manufacturer to wholesaler to pharmacy to consumer. Applying figures which Congress used to describe dosage units of a marketed product which has been diverted to a drug like MDMA is incorrect and misleading. MDMA is not a product which is marketed through the legitimate distribution system. There is no pharmaceutical manufacturer of MDMA. It is not carried by pharmaceutical wholesalers. It is not found in retail pharmacies. It is not prescribed by physicians. There are not millions of dosage units available for diversion. With the exception of the small 25/Drs. Greer and Grinspoon, et al. quoted on page 19 of their proposed findings the following from the House Committee Report:

The term "substantial" means more than a mere scintilla of isolated abuse, but less than a preponderance. Therefore, documentation that, say several hundred thousand dosage units of a drug have been diverted would be 'substantial' evidence of abuse despite the fact that tens of millions of dosage units of that drug are legitimately used in the same time period.

quantities prepared by a chemist for the psychiatrists who testified in this proceeding, all MDMA is clandestinely produced for clearly non-medical uses.

The agency has presented evidence of the increased availability and actual abuse of MDMA that extends back for several years. A DEA Special Agent testified as to MDMA's availability in the illicit market in Texas.<sup>26/</sup> A psychologist who conducts research and studies among drug abusers reported on the availability of MDMA in Southern California.<sup>27/</sup> Coupled with these reports were statistics gathered by DEA from its laboratories and from selected state and local and anonymous sampling laboratories. DEA witness Sapienza testified that these statistics are vastly underreported for substances that are noncontrolled because investigations involving non-controlled substances such as MDMA are not pursued.<sup>28/</sup> This was clearly shown by the agency's finding 53. From July 1, 1985 through September, 1985, at least 14 exhibits amounting to 35,000 dosage units of MDMA were submitted to DEA laboratories in Texas. Compare this four-month period to the 34 exhibits of MDMA submitted from 1972 through 1983. (A-B2).

The statistical reporting systems which include law enforcement laboratory submissions and the Drug Abuse Warning

26/Chester, direct.

27/Siegel, direct.

28/Sapienza, direct, p. 3

Network (DAWN), are not intended to provide quantitative evidence of the availability of a drug. One of their purposes is to be an indicator of a drug's presence in the illicit traffic and of its abuse.

DEA has introduced substantial evidence of actual abuse of MDMA. Although the amount of "diversion" of a legitimately marketed product may be determined since records are kept, the amount of MDMA available for abuse cannot be determined since there is no legitimate manufacturer. The presence of clandestine laboratories capable of manufacturing MDMA indicates that the amounts of MDMA available for abuse greatly exceed the several hundred thousand dosage units postulated as a threshold for control by Drs. Greer and Grinspoon, et al. The evidence strongly shows large-scale and significant use by individuals, all of it abuse, since there is no "accepted medical use" of the drug.

Drs. Greer and Grinspoon, et al. also discuss the legislative history in terms of the evolution of five schedules and the placement of amphetamines in Schedule III. There was much discussion regarding the abuse of amphetamines and methamphetamines during the hearings and even during the floor debate on the Comprehensive Drug Abuse Prevention and Control Act of 1970. What Drs. Greer and Grinspoon, et al. did not include in their findings however, was the language in the Conference Report of the House of Representatives which stated

as follows:

Amendments Nos. 4 and 5: These amendments proposed to transfer all amphetamines, phenmetrazine, and methylphenidate from schedule III to schedule II, thereby imposing stricter requirements for licensing of manufacturers, quota requirements, order forms, and other tighter controls, together with restrictions on the refilling of prescriptions, on these drugs.

The conference substitute limits this transfer to schedule II to liquid injectable methamphetamine, widely referred to as "speed." The legislation contains authority for the Attorney General to transfer drugs between schedules, upon making the appropriate findings and following the procedures prescribed in the legislation. It is the understanding of the managers that proceedings will be initiated involving a number of drugs containing amphetamines after the legislation has become law, but exceptions will be made for a number of amphetamine-containing drugs.<sup>29/</sup>

As Drs. Greer and Grinspoon, et al. noted, these substances were administratively placed in Schedule II by the Bureau of Narcotics and Dangerous Drugs. Amphetamine and methamphetamine were placed in Schedule II effective July 7, 1971.<sup>30/</sup> Phenmetrazine and methylphenidate were placed in Schedule II effective October 28, 1971.<sup>31/</sup> These actions occurred only a few months after the Comprehensive Drug Abuse Prevention and Control Act became effective on May 1, 1971. (Public Law 91-513, Section 1105). All of the products mentioned above had an "accepted medical use in the United States", and were lawfully and commercially marketed products.

<sup>29/</sup>H.R. Rep. No. 91-1603, 91st Cong., 2d Sess. 9 (1970)

<sup>30/36</sup> Fed. Reg. 12734 (July 7, 1971)

<sup>31/36</sup> Feb. Reg. 20686 (October 28, 1971)

No other substances which are in Schedule III are discussed extensively in the legislative histories. Congress realized the substantial abuse of these stimulant drugs and expected the BNDD to address the situation administratively.

Drs. Greer and Grinspoon, et al. discuss in their findings the concept of relative potential for abuse. The term "relative" naturally contemplates a comparison, a comparison with substances whose potential for abuse has been established. The drug or other substance in question is to be compared with a substance already controlled under the CSA. The statute itself delineates actual abuse from relative potential for abuse. The first of the eight factors listed in Section 811(c) which are to be considered by the Secretary and the Attorney General (Administrator) is "actual or relative potential for abuse" [Emphasis added.] It is clear that Congress intended relative potential for abuse to be considered separately from actual abuse. One of the ways in which Congress defined potential for abuse in the legislative history was that:

The drug or drugs containing such a 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...<sup>32/</sup>

MDMA has been shown to have pharmacological properties which closely resemble those of amphetamines and MDA, both drugs with demonstrated high potentials for abuse. MDMA has a

32/[1970] U.S. Code Cong. & Admin. News 4601

chemical structure very closely resembling MDA. Animals injected with MDMA have been shown to exhibit almost identical behavior to those injected with comparable doses of MDA.

High potential for abuse does not necessarily mean that individuals are dying from taking a specific drug. It does not necessarily mean that those who take the drug will experience instantaneous irreversible damage. What it means is that the drug or other substance has the same high potential to be a hazard to the public health and safety because of its pharmacology and data regarding its abuse as a substance with a known high abuse potential. In the instant case, there is ample data to establish that MDMA is pharmacologically similar to MDA and amphetamine. Further, there is considerable evidence of actual abuse of MDMA which has led individuals to seek medical care and treatment. MDMA has been associated with at least two deaths. It produces neurotoxicity in animals similar to that produced by MDA. Its long term effects have not been studied, but there is reason to believe that they will be similar to those produced by amphetamine-like compounds.

There is no need to repeat the facts which were presented by the agency in their findings of fact. Their message is clear. MDMA is recognized on the "street" as a desirable substance. It is clandestinely manufactured and marketed. It is not necessary or logical to compare the trafficking of MDMA quantitatively to other controlled substances. It is not realistic to compare it to substances which are marketed and

freely available in the commercial pharmaceutical market. Even as a non-controlled, non-approved substance, the evidence in the record indicates escalating abuse of MDMA in recent years. Pharm Chem Laboratories and Toxicology Testing Service, anonymous testing laboratories, received significantly more submissions in the period 1983 through 1985, than they had received in previous years. For the period May, 1983 to May, 1984, Pharm Chem Laboratories in California received 20 submissions identified as MDMA. For the period April, 1984 to March, 1985, Toxicology Testing Service in Florida received 19 submissions.

The pharmacological similarity of MDMA to drugs with established high potentials for abuse, coupled with the actual abuse and health hazards of MDMA evidenced by laboratory submissions, street trafficking, interviews with persons abusing it, and other data establishes a high abuse potential.

#### BIAS

In his argument that DEA failed to comply with the statutory requirements of 21 U.S.C. §811(b), Mr. Ehrnstein states that the Government lacked impartial objectivity, alleging that all those who participated in gathering and evaluating data within the Government were biased. Mr. Ehrnstein begins by challenging Mr. Sapienza's Analysis of MDMA. Mr. Ehrnstein says, "Mr. Sapienza based the DEA Analysis entirely on DEA enforcement reports and on reading literature."

He further goes on to say that Mr. Sapienza did not attempt to contact any psychiatrists who used MDMA in their practice or any authors of the studies he cited. At the time Mr. Sapienza conducted his analysis, and until the time that the comments were received from the Federal Register notice of proposed rulemaking published in July, 1984, neither Mr. Sapienza nor DEA were not aware that psychiatrists were using MDMA on human subjects.<sup>33/</sup> Mr. Sapienza utilized the data bases and published literature available, which is a logical method to gather data on abuse and abuse potential. These sources of information provide the data necessary to determine if there is a likelihood of abuse or potential for abuse of a specific substance.

Mr. Ehrnstein continues by charging that Dr. Tocus of the Food and Drug Administration was biased because he relied on the DEA Analysis and the files of the Food and Drug Administration in preparing his evaluation of MDMA. Mr. Ehrnstein contends that Dr. Tocus should have telephoned the authors of the papers cited to gather further information. He further alleges that the actions of Dr. Tocus and Mr. Sapienza amounted to "systematic exclusion of all statements favorable to MDMA." Mr. Sapienza and Dr. Tocus reviewed the available scientific and research data. They did this based upon the premise that legitimate research and scientific studies would be in the recognized scientific literature. It is neither

<sup>33/</sup> T-5, p. 107-108, Sapienza

reasonable nor logical to infer that Dr. Tocus or Mr. Sapienza had reason to know or even suspect that a few psychiatrists were utilizing MDMA. There was no data in any recognized literature which would have provided such an indication.

If a substance is being researched in humans, an IND application is required to be on file with the Food and Drug Administration.<sup>34/</sup> If such an application had been filed with the Food and Drug Administration by those utilizing MDMA in psychotherapy with humans, the data would have been available to Dr. Tocus and the Department of Health and Human Services for use in making their scientific and medical evaluation. The IND application would have been reviewed by chemists, physicians and pharmacologists with the FDA for proper documentation of safety and protocol requirements.<sup>35/</sup> Since no such applications were filed this type of data was not available to the Secretary.

Mr. Ehrnstein's argument that Mr. Sapienza and Dr. Tocus were biased in their evaluation of MDMA, and his assertion that this tainted the entire evaluation process is without merit. The requirements of 21 U.S.C. §811(b) were followed. All data which was reasonably available was included in the evaluation and was forwarded to the Assistant Secretary of Health for his consideration. The data which the Drug Enforcement

<sup>34/</sup>T-7, p. 103-104, Dr. Tocus

<sup>35/</sup>Tocus direct, p. 2-3.

Administration provided was evaluated by the Food and Drug Administration, and further attempts were made to gather data from available systems which would have disclosed the occurrence of recognized scientific research and clinical use of the drug.

#### RESEARCH

In their proposed findings, Drs. Greer and Grinspoon, et al. and Hoffmann-La Roche, Inc. discuss the negative impact upon research which they perceive as the result of placement of a drug or other substance in Schedule I. As discussed earlier in this response, Congress did consider the issue of research prior to the passage of the Comprehensive Drug Abuse Prevention and Control Act of 1970. Congressional committees heard testimony about substances which were undergoing research such as alphacetylmethadol. They heard testimony such as that presented by Dr. Jonathan Cole that placement of a drug in Schedule I would impede research and drug development. In spite of such testimony, Congress placed alphacetylmethadol in Schedule I. They also required the Department of Health and Human Services to review applications for research of Schedule I substances prior to the granting of such registration by the Drug Enforcement Administration.

There is no need to reiterate the recordkeeping and security requirements imposed upon Schedule I researchers as compared to researchers for substances in Schedule II-V. The agency outlined the similarities and differences in their proposed findings. Any individual conducting research with a controlled substance must be registered with the Drug

Enforcement Administration. All researchers must maintain complete and accurate records of controlled substances, take biennial inventories, and lock the substances in a substantially constructed cabinet. The main difference between conducting research with a Schedule I as opposed to other controlled substances is that before a registration for research in Schedule I will be granted by the Drug Enforcement Administration, the application and protocol must be reviewed by the Department of Health and Human Services. The reason for this is clear. The substances in Schedule I have no "accepted medical use in treatment in the United States." Congress also felt that the Department of Health and Human Services had the expertise necessary to review research protocols.

During the course of the hearings held before the House Subcommittee on Public Health and Welfare in February and March, 1970, Dr. Morris A. Lipton submitted a statement which was included in the record of those proceedings. Dr. Lipton appeared as a witness on behalf of Drs. Greer and Grinspoon, et al. in these proceedings. Dr. Lipton was concerned with the role of the Department of Justice in reviewing or approving the research of scientists. He said in this statement:

The shift of research responsibility to the Department of Justice is at best unnecessary and cumbersome and at worst dangerous. The pending bill requires that the Attorney General refer to the Secretary of HEW applications to engage in research on Schedule I drugs such as marijuana, LSD and heroin. The Secretary of HEW will then advise the Attorney General concerning the qualifications of the investigator, the institution

where it will be performed, the substances to be used and the research design. I grant that these things and more should be known before research is undertaken. The mechanism for learning about them already exists within the National Institutes of Health.<sup>36/</sup>

In expressing his concern for the role of the Department of Justice in the approval of research applications, Dr. Lipton made some significant comments concerning the requirements of research. How is an agency such as the Drug Enforcement Administration to determine whether legitimate researchers are applying to become registered to conduct research with Schedule I controlled substances? Congress properly left this role to an agency, the Department of Health and Human Services, which by Dr. Lipton's own admission has performed this function well.

Dr. Lipton also indicated in his remarks a point which the agency has tried to emphasize in this proceeding. Research on new drugs should continue with its goal the discovery of new therapeutic tools. In his statement to the Congressional committee in 1970, Dr. Lipton also stated:

I should like to close by emphasizing that research on drugs is and always will be an ongoing enterprise. We may expect in the next decade the synthesis or discovery of new agents that will be powerful agents in the treatment of mental disease, mental retardation and many physical diseases. In the process of generating these, we will very likely encounter new drugs which do both good and harm, depending upon how and on whom they are used. There is no way of predicting effects

<sup>36/</sup>Part I, Drug Abuse Control Amendments-1970: Hearings Before the Subcomm. on Public Health and Welfare of the House Comm. on Interstate and Foreign Commerce, 91st Cong., 2d Sess. (1970), p. 447 (Statement of Dr. Morris A. Lipton)

except thorough empirical research by responsible investigators. There is no way of a priori separating long term effects from immediate effects.<sup>37/</sup>

There is no opposition to MDMA as a potential or possible therapeutic tool. Research into such potential and the effects of the drug should be conducted. A mechanism has been provided in the Controlled Substances Act and the Food, Drug and Cosmetic Act to allow for such research. When the therapeutic potential of MDMA is examined in light of scientifically conducted research studies in both animals and humans, and a new drug application is approved for the drug, then it can be reexamined for possible placement in a schedule other than Schedule I of the Controlled Substances Act.

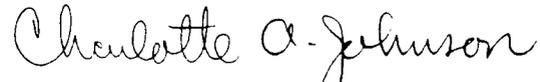
<sup>37/</sup>Id. p. 448

CONCLUSION

The evidence in the record in this proceeding amply demonstrates that 3,4-methylenedioxymethamphetamine (MDMA) is a substance which should be controlled pursuant to the Controlled Substances Act. It is a substance which has no "accepted medical use in treatment in the United States." It has a high potential for abuse, and there is evidence of escalating and widespread actual abuse. MDMA lacks accepted "safety for use under medical supervision," since its safety has never been established. MDMA should properly be placed in Schedule I of the Controlled Substances Act.

Respectfully submitted,

  
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Dated: February 10, 1986

CERTIFICATE OF SERVICE

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