IN THE

UNITED STATES COURT OF APPEALS

FOR THE FIRST CIRCUIT

LESTER GRINSPOON, Petitioner, v. DRUG ENFORCEMENT ADMINISTRATION, Respondent.	)	No. 86-2007

PETITION FOR REVIEW OF FINAL ORDER
OF DRUG ENFORCEMENT ADMINISTRATION

JOINT APPENDIX

Harry S. Harbin, Esq.
Charlotte A. Johnson, Esq.
U.S. Department of Justice
Washington, D.C. 20537

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January 12, 1987

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U.S. Department of Justice

Drug Enforcement Administration

Washington, D.C. 20537

DEC 3 1986

Francis P. Scigliano, Esquire
Clerk, U. S. Court of Appeals
for the First Circuit
1606 John W. McCormack Post Office
and Courthouse
Boston, Massachusetts 02109

Re: Lester Grinspoon, M.D.,
Petitioner,

v.

Drug Enforcement Administration,
Respondent.
No. 86-2007

Dear Mr. Scigliano:

I hereby certify, pursuant to Rule 17(b) of the Federal Rules of Appellate Procedure, that the enclosed copy of the Administrative Law Judge Docket Card contains a list of all documents, transcripts of testimony, exhibits and other material comprising the record in this matter.

Very truly yours,

John C. Lawn

John C. Lawn
Administrator

Enclosure

cc: Lester Grinspoon, M.D. (with enclosure)
Boston, Massachusetts

Harry S. Harbin, Esquire (with enclosure)
U. S. Department of Justice

000001

Administrative Law Judge Docket Card

Docket No.	Respondent, Name & Address	Attorney, Name & Address
84-48	MDMA Scheduling	An "*" appears in item 1 below before the name of each individual who requested a hearing

Date of Rule to Show Cause or other DEA action Appealed from	Date of Request for Hearing	Date Request Received by Hearing Clerk

Government Counsel Stephen E. Stone, Esq. & Charlotte A. Johnson, Esq.

Item #	Date	Entry
1	11-13-84	Memorandum to Judge from Deputy Administrator, DEA, transmitting the following:
		Notice of proposed rulemaking (scheduling) as published on 7-27-84 at 49 Fed. Reg. 30210
		Comments and/or requests for hearing received from the following: a. Joseph Downing, M.D.
		*b. Thomas B. Roberts, Ph.D. c. Lindsay O. Robinson d. Donald L. Darling
		e. David E. Nichols, Ph.D. *f. Rodney A. Houghton, M.D. *g. George Greer, M.D.
		h. June E. Riedlinger, R.Ph. *i. David B. Katzin, M.D., Ph.D. *j. Lester Grinspoon, M.D. & James Bakalar
		k. C. Quincy, D.O. l. Joel Alter, D.O. m. Assn. for Responsible Use of Psycho-Actives
		*n. Peter G. Bennett, M.D. o. Nathaniel Branden, Ph.D. *p. Alexander T. Shulgin, Ph.D.
2	11-20-84	Copy of letter to Administrator, DEA, from counsel for Roberts, Greer, Grinspoon & Bakalar
3	12-31-84	Notice of hearing dated 12-21-84 as published at 49 Fed. Reg. 50732
4	1-4-85	Letter (notice of appearance) to Judge from counsel for DEA

(continued on reverse)

Item #	Date	Entry
5	1-29-85	Letter (notice of appearance) to Hearing Clerk from Lyn B. Ehrnstein, Esq.
6	1-30-85	Letter (notice of appearance) to Hearing Clerk from David E. Joranson
7	1-30-85	Letter (notice of appearance) to Hearing Clerk from Robert T. Angarola, Esq. & Robert A. Dormer, Esq. as counsel for Hoffmann-LaRoche Inc. & McNeilab, Inc.
8	2-1-85	Preliminary hearing session held - Washington, D.C.
9	2-6-85	Transcript of 2-1-85 session received
10	2-8-85	Memorandum To Participants
11	2-8-85	Memorandum And Order
12	3-11-85	Response Of Hoffmann-LaRoche Inc. And McNeilab, Inc. To Memorandum And Order Of February 8, 1985
13	3-11-85	Opening Memorandum On Behalf Of Drs. Greer And Grinspoon, Professors Bakalar And Roberts
14	3-11-85	Government's Prehearing Statement
15	3-12-85	Letter to Hearing Clerk from Lyn B. Ehrnstein t/w Response To Memorandum And Order
16	3-22-85	Memorandum To Counsel
17	3-26-85	Letter to Judge from counsel for Hoffmann-LaRoche & McNeilab
18	3-27-85	Letter to Judge w/ Statement from David E. Joranson
19	3-27-85	Letter to Judge from counsel for Greer, Grinspoon, Bakalar & Roberts
20	3-27-85	Memorandum To The Parties
21	3-29-85	Memorandum To The Parties

Administrative Law Judge Docket Card

Docket No.	Respondent, Name & Address	Attorney, Name & Address
84-48	MDMA Scheduling	

Date of Rule to Show Cause or other DEA action Appealed from	Date of Request for Hearing	Date Request Received by Hearing Clerk

Government Counsel Stephen E. Stone, Esq. & Charlotte A. Johnson, Esq.

Item #	Date	Entry
22	4-1-85	Letter to Judge from David E. Joranson
23	4-2-85	Memorandum To The Parties
24	4-8-85	Letter to Judge from L. B. Ehrnstein transmitting Second Brief and Request To DEA For Copies Of Documents
25	4-8-85	First Memorandum Of Law Submitted on Behalf of Drs. Grinspoon & Greer, Professors Bakalar & Roberts
26	4-8-85	Memorandum On Behalf Of Hoffmann-LaRoche, Inc. and McNeilab, Inc.
27	4-9-85	Copy of letter to counsel for Drs. Grinspoon & Greer, Pfsrs. Bakalar & Roberts from counsel for DEA
28	4-11-85	Request for Production of Documents filed by counsel for Hoffmann-LaRoche & McNeilab
29	4-15-85	Copy of letter from counsel for DEA to counsel for all other parties
30	4-17-85	Letter to Addressees from Lyn B. Ehrnstein, Esq.
31	4-17-85	Memorandum To The Parties
32	4-18-85	Copy of letter to Lyn B. Ehrnstein, Esq. from counsel for DEA

(continued on reverse)

Item #	Date	Entry
33	4-19-85	Letter to Judge from David E. Joranson, WI Cont. Sub. Board
34	4-22-85	Government's First Memorandum Of Law
35	4-25-85	Direct Testimony Of David E. Joranson (returned to Joranson for signature)
36	4-25-85	Final Witness List of Hoffmann-LaRoche and Statement of witness
37	4-25-85	Testimony Submitted On Behalf Of Grinspoon, Greer, Bakalar & Rober
38	4-25-85	Letter to Judge from counsel for DEA
39	4-25-85	Letter to Judge from Robert Randall
40	4-26-85	Letter to Judge from counsel for DEA transmitting Identification Of Witnesses And Affidavits Of Direct Testimony
41	4-29-85	Letter to Judge from Lyn B. Ehrnstein transmitting Reply Brief
42	4-29-85	Letter to Judge from counsel for DEA transmitting affidavit
43	4-29-85	Reply Memorandum On Behalf Of Hoffmann-LaRoche, Inc. and McNeilab, Inc.
44	4-29-85	Reply Memorandum Submitted On Behalf Of Greer, et al.
45	4-29-85	Letter to Judge from counsel for Greer, et al., requesting extension of time & Judge's "Request granted" notation
46	4-30-85	Order For Corrections To The Transcript
47	4-30-85	Letter to Robert Randall from Hearing Clerk
48	4-30-85	Letter to Judge from David E. Joranson transmitting signed sworn Direct Testimony
49	4-30-85	Government's Final List Of Documents

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Government Counsel Stephen E. Stone, Esq. & Charlotte A. Johnson, Esq.

Item #	Date	Entry
50	4-30-85	Supplements To Testimony Submitted On Behalf Of Greer, et al.
51	5-2-85	Letter to All Participants Of Record from Hearing Clerk
52	5-2-85	Copy of letter to counsel for Greer, et al., with attachment from Government counsel
53	5-6-85	Final List Of Documents filed by counsel for Greer, et al.
54	5-8-85	Signed Direct Testimony Of J. E. Riedlinger, R.Ph., filed by counsel for Greer, et al.
55	5-9-85	Copy of letter from Government counsel to Lyn B. Ehrnstein, Esq.
56	5-9-85	Copy of letter from Government counsel to assistant to counsel for Greer, et al.
57	5-10-85	Copy of letter to counsel for Greer, et al., from David E. Joranson
58	5-13-85	Second Supplements To Testimony Submitted On Behalf Of Greer, et al.
59	5-16-85	Memorandum To The Parties
60	5-20-85	Government's Rebuttal Testimony

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Item #	Date	Entry
61	5-21-85	Copy of letter to counsel for Greer, et al. from Lyn B. Ehrnstein
62	5-28-85	Letter to Judge from counsel for DEA
63	5-29-85	Memorandum To Counsel
64	5-30-85	Memorandum to Judge from Acting Administrator, DEA, with attachment, typed version of Notice of Emergency Scheduling
65	5-31-85	Notice of Temporary Placement of MDMA Into Schedule I as published at 50 Fed. Reg. 23118-23120
66	5-31-85	Government's List Of Witnesses For Cross-Examination
67	6-1-85	Judge's Opinion And Recommended Decision On Preliminary Issue
68	6-3-85	Cross-Examination Of Witnesses filed by counsel for Greer, et al.
69	6-6-85	Letter to Judge from counsel for Greer, et al., w/ attachments
70	6-10-85	Hearing session held - Los Angeles, CA
71	6-14-85	Rebuttal Testimony received from counsel for Greer, et al.
72	6-14-85	Letter to counsel for Hoffmann-LaRoche Inc. & McNeilab, Inc. from Hearing Clerk transmitting set of ALJ Exhibits
73	6-14-85	Letter to David E. Joranson from Hearing Clerk transmitting set of ALJ Exhibits
74	6-24-85	Letter to Hearing Clerk from counsel for Greer, et al., transmitting set of exhibits
75	6-24-85	Transcript of hearing session held 6-10-85 received
76	6-24-85	Memorandum To Participants
77	6-26-85	Letter to Judge from Lyn B. Ehrnstein, Esq.

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Docket No.	Respondent, Name & Address	Attorney, Name & Address
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Date of Rule to Show Cause or other DEA action Appealed from	Date of Request for Hearing	Date Request Received by Hearing Clerk

Government Counsel Stephen E. Stone, Esq. & Charlotte A. Johnson, Esq.

Item #	Date	Entry
78	6-27-85	Letter to Lyn B. Ehrnstein, Esq. from Hearing Clerk
79	7-2-85	Letter to Judge from David E. Joranson
80	7-3-85	Letter to the Acting Administrator, DEA, from Judge transmitting Opinion & Rec. Dec. on Preliminary Issue
81	7-3-85	Copy of letter to counsel for Greer, et al, from Government counsel
82	7-3-85	Letter to Judge from Government counsel
83	7-8-85	Letter to Judge from David E. Joranson transmitting amendment to Direct Testimony
84	7-10 & 7-11-85	Hearing session held - Kansas City, MO
85	7-10-85	Copy of letter from counsel for Greer, et al, to Government counsel
86	7-12-85	Letter to Acting Administrator, DEA, from Judge
87	7-12-85	Correction to notice re: temporary scheduling of MDMA published at 50 Fed. Reg. 28395
88	7-18-85	Letter to Judge from counsel for McNeilab, Inc. & Hoffmann-LaRoche Inc.

(continued on reverse)

Item #	Date	Entry
89	7-19-85	Copy of letter to counsel for Greer, et al, from Government counsel
90	7-22-85	Motion For Leave To File Add'l Documents filed by counsel for Greer, et al, t/w set of documents
91	7-23-85	Transcript of hearing sessions held 7-10 and 7-11-85 received
92	7-23-85	Letter to Hearing Clerk from secretary to counsel for Greer, et al, transmitting Exhibits 16 and 17
93	7-24-85	Letter to Judge from Government counsel
94	7-24-85	Request For Cross-Examination By Deposition filed by Government counsel
95	7-26-85	Memorandum To Participants
96	7-30-85	Government's Exceptions To Judge's Opinion and Recommended Decision on Preliminary Issue
97	8-1-85	Memorandum To Participants
98	8-1-85	Memorandum To Participants
99	8-6-85	Letter to Roger Walsh, Univ. of CA, Irvine, CA, from Hearing Clerk returning his letter dated 7-31-85
100	8-9-85	Memorandum To The Parties
101	8-12-85	Letter to Judge from Government counsel
102	8-13-85	Memorandum To The Parties
103	8-15-85	Government's Request For Leave To File An Additional Document
104	8-15-85	Response on Behalf of Drs. Greer, et al, to Agency Counsel's Exceptions to Preliminary Decision
105	8-15-85	Exceptions To The Opinion & Recommended Decision on Preliminary Issue filed by counsel for Hoffmann-LaRoche & McNeilab
106	8-20-85	Letter to the Administrator, DEA, from Judge transmitting exceptions and responses thereto

Administrative Law Judge Docket Card

Docket No.	Respondent/Name/Address	Attorney, Name & Address
84-48	MDMA Scheduling	

Date of Rule to Show Cause or other DEA action Appealed from	Date of Request for Hearing	Date Request Received by Hearing Clerk

Government Counsel Stephen E. Stone, Esq. & Charlotte A. Johnson, Esq.

Item #	Date	Entry
107	8-23-85	Copy of letter to the Administrator, DEA, from Government counsel
108	8-23-85	Response of Drs. Greer, et al., to Request By Agency Staff To Admit WHO Document Into The Record
109	8-23-85	Letter to the Administrator, DEA, from Judge
110	8-26-85	Copy of letter from Government counsel to all other parties
111	8-26-85	Letter to Judge from Morris A. Lipton, Ph.D. (witness for Greer, et al.)
112	8-27-85	Memorandum To Counsel
113	9-6-85	Information Concerning WHO Proceedings For Scheduling MDMA Under The Convention On Psychotropic Substances filed by Government counsel
114	9-19-85	Copy of letter to counsel for Hoffmann-LaRoche & McNeilab from Government counsel
115	9-23-85	Copy of letter to counsel for Greer, et al, from Government counsel
116	10-3-85	Copy of letter to counsel for Greer, et al, from Government counsel, with attachment
117	10-7-85	Letter to Judge from Administrator, DEA, returning Judge's opinion on "Preliminary Issue"

(continued on reverse)

Item #	Date	Entry
118	10-8 - 10-11-85	Hearing session held - Washington, DC
119	10-17-85	Copy of letter to all other participants from Government counsel
120	10-17-85	Deposition of Richard Arthur Glennon, Ph.D., filed by Government counsel
121	10-18-85	Memorandum To The Participants
122	10-18-85	Letter to Judge from Government counsel
123	10-18-85	Request To Replace Government Exhibit B-22 With Corrected Document filed by Government counsel
124	10-21-85	Letter to Messrs. Ehrnstein and Joranson from Hearing Clerk
125	10-21-85	Letter to counsel for Hoffmann-LaRoche Inc. and McNeilab, Inc. from Hearing Clerk
126	10-21-85	Transcripts of hearing sessions held 10-8 & 10-10-85 received
127	10-22-85	Order
128	10-23-85	Copy of letter to counsel for Greer, et al, from Government counsel with attachment
129	10-23-85	Copy of letter to counsel for Greer, et al, from Government counsel with attachments (FDA documents)
130	10-25-85	Copy of letter to Government counsel from counsel for Greer, et al
131	10-25-85	Declaration of Richard Ingrasci, M.D. filed by counsel for Greer
132	10-25-85	Request for Additional Time To Submit Comments on Agency Exhibits B-21, B-22 and B-23 filed by counsel for Greer, et al and Judge's "Request granted" notation
133	10-25-85	Letter to Judge from Government counsel with attachment
134	10-25-85	Government's Request For Leave To File An Additional Document

Administrative Law Judge Docket Card

Docket No.	Respondent, Name & Address	Attorney, Name & Address
84-48	MDMA Scheduling	

Date of Rule to Show Cause or other DEA action Appealed from	Date of Request for Hearing	Date Request Received by Hearing Clerk

Government Counsel Stephen E. Stone, Esq. & Charlotte A. Johnson, Esq.

Item #	Date	Entry
135	10-28-85	Request For Rebuttal Testimony By Edward C. Tocus, Ph.D. filed by Government counsel
136	10-28-85	Letter to Judge from Government counsel with attachment
137	10-31-85	Letter to Judge from counsel for Hoffmann-LaRoche and McNeilab
138	10-31-85	Objection To Agency Request Re Tocus Rebuttal Testimony filed by counsel for Greer, et al
139	11-1-85	Hearing session held - Washington, DC
140	11-1-85	Response to Agency Exhibits B-21, B-22 and B-23 filed by counsel for Greer, et al
141	11-6-85	Letter to Judge from counsel for Greer, et al, transmitting corrected copy of #139 above
142	11-6-85	Request to File Additional Document filed by counsel for Greer, et al
143	11-8-85	Government's Objections To Response Of Drs. Greer and Grinspoon, et al, to Agency Exhibits B-21, B-22 and B-23
144	11-8-85	Government's Objections To Request Of Drs. Greer and Grinspoon, et al, To File An Additional Document
145	11-12-85	Memorandum To The Parties

(continued on reverse)

Item #	Date	Entry
146	11-12-85	Memorandum And Order
147	11-12-85	Copy of letter to Agency counsel from counsel for Greer, et al, with attachment
148	11-15-85	Copy of letter to counsel for Greer, et al, from Agency counsel with attachment
149	11-19-85	Transcript of hearing session held 11-1-85 received
150	11-20-85	Letter to Judge from counsel for Hoffmann-LaRoche and McNeilab requesting opportunity to file proposed findings & conclusions & Judge's "Request granted" notation
151	11-25-85	Submission By Drs. Grinspoon, Greer, et al. In Response To Agency Exhibit B-25
152	11-29-85	Letter to Judge from David E. Joranson
153	12-5-85	Notice Of Filing Of Exhibit 59 By Drs. Grinspoon, Greer, et al. (t/w document, Exhibit 59)
154	12-6-85	Proposed Corrections To Transcript filed by counsel for Hoffmann-LaRoche Inc. and McNeilab, Inc.
155	12-10-85	Government's Proposed Findings Of Fact, Conclusions Of Law And Argument
156	1-10-86	Proposed Findings Of Fact And Conclusions Of Law With Supporting Statement Of Reasons Submitted By Lyn B. Ehrnstein
157	1-15-86	Brief, Including Proposed Findings Of Fact And Conclusions Of Law filed by counsel for Greer, et al
158	(1-15-86) 1-16-86	Letter from counsel transmitting Hoffmann-LaRoche's Proposed Findings Of Fact, Conclusions Of Law And Argument
159	1-23-86	Memorandum To The Parties
160	2-3-86	Letter to Hearing Clerk from counsel for Hoffmann-LaRoche & McNeilab
161	2-10-86	Government's Response To The Findings Of Fact, Conclusions Of Law & Arguments of other parties
162	2-14-86	Oral argument held - Washington, D.C.

Administrative Law Judge Docket Card

Docket No.	~~Respondent's Name & Address~~	Attorney, Name & Address
84-48	MDMA Scheduling	

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Government Counsel Stephen E. Stone, Esq. & Charlotte A. Johnson, Esq.

Item #	Date	Entry
163	2-14-86	Errata Sheet For Brief On Behalf Of Drs. Greer, Grinspoon, et al. (received at oral argument)
164	2-21-86	Transcript of oral argument received
165	3-13-86	Proposed Corrections To Transcript filed by counsel for Hoffmann-LaRoche & McNeilab
166	3-14-86	Memorandum To The Participants
167	3-31-86	Agency's Proposed Corrections To The Transcript
168	5-1-86	Memorandum To The Parties
169	5-13-86	Memorandum To The Parties
170	5-22-86	Judge's Opinion and Recommended Decision
171	6-9-86	Letter to Judge from Government counsel requesting extension of time & Judge's "Request granted" notation
172	6-9-86	Request For Opportunity To Respond To Exceptions filed by counsel for Greer, Grinspoon, et al.
173	6-11-86	Exception To Opinion And Ruling filed by David E. Joranson

(continued on reverse)

Item #	Date	Entry
174	6-13-86	Government's Exceptions To Judge's Opinion & Recomm. Decision
175	6-17-86	Notice of Extension of Temporary Control of MDMA (dated 6-12-86) as published at 51 Fed. Reg. 21911 (1986)
176	6-20-86	Letter to Judge from counsel for Drs. Greer, Grinspoon, et al, requesting time to file response to Government's Exceptions & Judge's "Request granted" notation
177	6-20-86	Exceptions To Judge's Opinion and Recommended Decision on Issue No. 2 filed by counsel for Hoffmann-LaRoche Inc.
178	6-27-86	Response Of Grinspoon, Greer, et al to Government's Exceptions; Motion To Strike Portions Of Government's Exceptions; and Request For Opportunity For Oral Presentation To The Administrator
179	6-30-86	Letter to Judge from counsel for Grinspoon, Greer, et al, transmitting corrected copy of Response To Government's Exceptions
180	7-18-86	Order For Corrections To The Transcript
181	7-24-86	Letter to the Administrator, DEA, from Judge transmitting record
182	7-28-86	Letter to Judge (notice of appearance) from new co-counsel for Drs. Greer, Grinspoon, et al
183	8-11-86	Order (of the Administrator)
184	8-21-86	Government's Exceptions To Judge's Opinion (refiled)
185	10-14-86	Administrator's Final Order (dated 10-8-86) published at 51 Fed. Reg. 36552 (1986)

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. 84-48]

Schedules of Controlled Substances; Scheduling of 3,4-Methylenedioxymethamphetamine (MDMA) into Schedule I of the Controlled Substances Act

AGENCY: Drug Enforcement Administration, Justice.

ACTION: Final rule.

SUMMARY: This is a final rule placing the drug 3,4-methylenedioxymethamphetamine (MDMA) into Schedule I of the Controlled Substances Act (CSA). MDMA will be classified as a hallucinogenic controlled substance. This action was initiated following the Drug Enforcement Administration's (DEA) review of the abuse and illicit trafficking of MDMA. The Assistant Secretary for Health, Department of Health and Human Services (DHHS), supported DEA's position that the substance be placed into Schedule I of the CSA. The effect of this rule is to impose the criminal sanctions and regulatory controls of Schedule I on the manufacture, distribution and possession of MDMA.

DATE: The effective date of this order is November 13, 1986.

SUPPLEMENTARY INFORMATION: On March 13, 1984, the Administrator of the Drug Enforcement Administration submitted information relevant to the abuse potential and illicit trafficking of 3,4-methylenedioxymethamphetamine (MDMA) to the Assistant Secretary for Health, Department of Health and Human Services. Briefly, the information documented that 3,4-methylenedioxymethamphetamine, trafficked on the street as MDMA or "Ecstasy": (1) Is an analog of the Schedule I controlled substance, 3,4-methylenedioxyamphetamine (MDA), (2) has no legitimate medical use or manufacturer in the United States, (3) has been clandestinely synthesized and encountered in the illicit drug traffic, (4) produces stimulant and psychotomimetic effects in humans similar to those produced by MDA, and (5) has been associated with medical emergencies as reported by the Drug Abuse Warning Network (DAWN).

In accordance with the provisions of 21 U.S.C. 811(b), the DEA Administrator requested a scientific and medical evaluation of the relevant information and a scheduling recommendation for 3,4-methylenedioxymethamphetamine from the Assistant Secretary for Health. On June 6, 1984, the Administrator of the Drug Enforcement Administration received a letter from the Assistant Secretary for Health, acting on behalf of the Secretary of the Department of Health and Human Services, stating that 3,4-methylenedioxymethamphetamine (MDMA) has a high potential for abuse and presents a significant risk to the public health, and recommending that it should be placed into Schedule I of the Controlled Substances Act.

On July 27, 1984, the Administrator of the Drug Enforcement Administration, based upon a review of investigations by the Drug Enforcement Administration and relying on the scientific and medical evaluation and the recommendation of the Secretary of Health and Human Services in accordance with 21 U.S.C. 811(c), issued a Notice of Proposed Rulemaking to amend § 1308.11 of Title 21 of the Code of Federal Regulations by placing MDMA in Schedule I as a hallucinogenic controlled substance. 49 FR 30210. MDMA was not, at that time, a controlled substance.

The Notice of Proposed Rulemaking allowed sixty days for interested parties to submit comments, objections or requests for a hearing.

Sixteen comments were received in response to the notice, seven of which requested a hearing.

These comments and requests for hearing came from a variety of physicians, counselors, instructors and others in medical or health care related professions, as well as from former subjects of experimental studies involving the use and effects of MDMA.

All of the persons or entities that submitted comments and/or requests for hearing opposed the proposed placement of the substance into Schedule I. DEA was urged by many to delay this proposed action until after additional research could be completed. Most felt that preliminary usage and studies had shown MDMA to have enormous potential value as an adjunct to psychotherapy, as an analgesic and in the treatment of problems of drug addiction.

Most of the writers vigorously objected to one of DEA's stated bases for the proposed scheduling, that being the finding that MDMA had no currently accepted medical use in treatment in the United States. Some of the responding physicians and psychiatrists reported having used it in their practices with what they felt were positive results. Many disputed the Agency's concept of "currently accepted medical use."

Several stated that the highly restrictive scheduling which was contemplated would effectively end presently ongoing research and scientific experimentation. Some felt that the costs involved in obtaining an Investigational New Drug permit from the Food and Drug Administration to conduct human research with a Schedule I drug would be prohibitive to any individual researcher. Another stated that it would be unrealistic to believe that any pharmaceutical company would develop the drug.

Several felt that DEA did not have sufficient information regarding the present and potential uses of this drug and urged that the proposed scheduling action be delayed until DEA had the opportunity to consider additional studies and reports of experimentation and research.

A few of the writers questioned the finding of high abuse potential as a basis for placement into Schedule I. While most of them acknowledged that there is some evidence of unsupervised use of MDMA, they felt the reported instances of abuse were not sufficient in number to warrant the conclusion that it is a substance with a high potential for abuse. Others stated that a potential for abuse had not led DEA to place certain other substances into Schedule I. A few believed that there may be some confusion of this substance with another which is known to be abused, MDA, and that the differences between the two should be closely examined. A number of the writers were not opposed to the placement of MDMA into one of the schedules under the CSA, but believed that Schedule I was not the appropriate schedule.

On November 13, 1984, the Deputy Administrator of DEA referred the matter to the Agency's Administrative Law Judge, Francis L. Young, to conduct a hearing for the purpose of receiving factual evidence and expert opinion regarding the proposed scheduling of MDMA. Judge Young was directed to report to the Administrator of DEA his findings and recommended conclusions on the appropriate scheduling action to be taken with respect to MDMA and on the question of whether a drug which has potential for abuse but no currently accepted medical use in treatment can lawfully be placed in any schedule other than Schedule I. The proceeding was

conducted "on the record after opportunity for a hearing" as required by 21 U.S.C. 811(a) and in accordance with the Administrative Procedures Act. 5 U.S.C. 556 and 557.

The authority and criteria for classifying substances into schedules under the Controlled Substances Act is found in 21 U.S.C. 811. This section of the Act sets forth the standards by which the Attorney General and the Secretary of the Department of Health and Human Services are to evaluate substances for control, decontrol or rescheduling. The Secretary of DHHS is charged with making scientific and medical evaluations, including scientific evidence of a substance's pharmacological effects, the state of current scientific knowledge regarding the drug or other substance, what risk there is to the public health, the psychic or physiological dependence liability of the drug, and whether the substance is an immediate precursor of a substance already controlled under the Act. The Attorney General must consider those items presented by the Secretary, and in addition must consider the actual or relative potential for abuse of the substance, the history and current pattern of abuse, and the scope, duration and significance of abuse. MDMA was not a controlled substance. It had not been approved for marketing in the United States by the Food and Drug Administration.

Following prehearing procedures, there remained five parties, including the Agency, participating in the hearing process. The participants were the Agency staff; George Greer, M.D., Lester Grinspoon, M.D., Thomas B. Roberts, Ph.D. and James Bakalar; McNeilab, Inc. and Hoffmann-LaRoche, Inc.; Lyn B. Ehrnstein, Esq.; and David E. Joranson.

Five hearing sessions, compromising nine hearing days, beginning on February 1, 1985, and culminating on November 1, 1985, were conducted before the Administrative Law Judge; the testimony of 33 witnesses was heard and 95 exhibits were received into evidence.

At a preliminary prehearing conference on February 1, 1985, the Administrative Law Judge determined that one of the issues identified presented a purely legal question which might be decided without the need of any evidence and in advance of the other issues in the case. The issue was:

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 than Schedule I?

After studying briefs submitted by the participants, the judge issued a recommended decision on that issue, dated June 1, 1985. He recommended, first, that the language of the Act was such that a substance with a potential for abuse less than a "high" potential, and having no currently accepted medical use in treatment, cannot be placed in *any* of the five schedules. Alternatively, the judge recommended that such a substance should be placed in either Schedule III, IV or V, depending upon its degree of potential for abuse. In a letter to the Administrative Law Judge, dated October 7, 1985, the Administrator advised that he had decided not to issue a final agency ruling on that initial ruling until he had received the entire record at the conclusion of the case.

During the course of the hearing, on July 1, 1985, in an independent action by the Administrator of DEA, MDMA was placed into Schedule I of the CSA pursuant to the emergency scheduling provisions of 21 U.S.C. 811(h)(1), following a determination by the Administrator that this action was necessary to avoid an imminent hazard to the public safety. 50 FR 23118.

On May 22, 1986, the judge issued his Opinion and Recommendations regarding the scheduling of MDMA. The judge recommended that MDMA be placed in Schedule III of the CSA. He reached this conclusion after finding that MDMA has a currently accepted medical use in treatment in the United States, that MDMA does not lack accepted safety for use under medical supervision, and that it has less than a high potential for abuse.

Concerning the issue of "accepted medical use", the judge refused to accept the Agency's argument that if a drug or other substance being considered for scheduling is not approved for marketing in the United States under the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 301, *et seq.*, then it has no "accepted medical use." He concluded that "accepted medical use" is determined by what is actually going on within the health care community. Using this standard, the judge found that, based on the testimony of a relatively small group of psychiatrists and psychotherapists who have used MDMA in treatment of humans and found it to have certain desirable effects, MDMA had an accepted medical use in treatment in the United States. With regard to the issue of "accepted safety for use", the judge concluded that MDMA does not lack accepted safety for use because the same group of psychiatrists and psychotherapists mentioned above have administered MDMA to willing subjects in uncontrolled, nonresearch studies and would not have done so if such a procedure was unsafe. Finally, with regard to the issue of abuse potential, the judge found that the Agency did not meet its burden in establishing that MDMA has a high potential for abuse.

On June 11, 13 and 24, 1986, respectively, David Joranson, counsel for DEA, and two counsel for Hoffman-LaRoche, Inc. filed exceptions to the Opinion and Recommendations of the Administrative Law Judge. In reply, Grinspoon, Greer, et al. filed a Response to the exceptions on June 27, 1986, and also moved to strike portions of the Government's exceptions alleging the Government's use of the term "bias" with respect to the Administrative Law Judge's opinion was prejudicial. Additionally, they filed a motion for the opportunity for oral presentation to the Administrator. On July 24, 1986, the Administrative Law Judge certified and transmitted the record to the Administrator of DEA. The record included the Opinion and Recommendations of the Administrative Law Judge, the findings of fact and conclusions of law proposed by all parties, the exceptions filed by the parties, the response to those exceptions and motions filed by Grinspoon, Greer, et al., all of the exhibits and affidavits, and all of the transcripts of the hearing sessions.

On August 11, 1986, the Administrator granted the motion to strike portions of the Government exceptions, filed by Grinspoon, Greer, et al., and ordered the Government to refile its exceptions without use of the term "bias" with respect to the Administrative Law Judge's opinion. The Administrator also denied the motion for the opportunity for oral presentation to him filed by Grinspoon, Greer, et al. On August 21, 1986, the Government refiled its exceptions.

The Administrator has carefully reviewed the entire record in this matter and hereby issues this final rule as prescribed by 21 CFR 1316.67. The Administrator declines to accept the recommendations of the Administrative Law Judge and finds that there is substantial evidence in the record to support the decision that MDMA be placed in Schedule I as a hallucinogenic controlled substance. The Administrator finds, consistent with his decision that:

1. A new drug application (NDA) must be approved by the Food and Drug Administration prior to the marketing of a new drug in the United States. The NDA generally consists of data collected during the pre-clinical and

investigational new drug (IND) processes. 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.

2. 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)).

3. 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.

4. Before an unmarketed new drug may be tested on humans, an investigational new drug exemption (IND) must be applied for 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.

5. 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 human tests.

6. 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 FR 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 FR 28150)

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.

7. In March 1984, there was no reference in the files of the Food and Drug Administration to the substance 3,4-methylenedioxymethamphetamine (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 was not a grandfathered drug and that it had not been approved for over-the-counter use.

8. 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.

9. 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.

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

11. 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.

12. 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 two weeks to three months.

13. 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.

14. 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.

15. 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 FR 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). Because 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 FR 28152)

16. There is no legitimate commercial manufacturer of MDMA in the United States. Further, the MDMA which has been used by psychiatrists is not labeled with safety or therapeutic considerations.

17. 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.

18. Accordingly, the Administrator finds that 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."

19. MDMA, or 3,4-methylenedioxymethamphetamine, belongs to a class of compounds which can be termed phenethylamines or, narrowly defined, phenylisopropylamines or amphetamines.

20. MDA, or 3,4-methylenedioxyamphetamine, amphetamine and methamphetamine are also phenylisopropylamines.

21. MDA, or 3,4-methylenedioxyamphetamine, is formed by the addition of a methylenedioxy group to amphetamine.

22. MDMA is formed by the addition of a methylenedioxy group to methamphetamine.

23. The addition of a methylenedioxy group to the aromatic nucleus of amphetamines produces compounds with psychotomimetic activity.

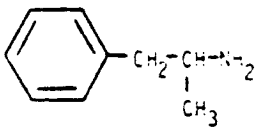
24. Psychotomimetic is a term used to describe a large class of compounds which change or modify a person's mood or mental state. The terms psychotomimetic and hallucinogenic are commonly used interchangeably.

25. 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.

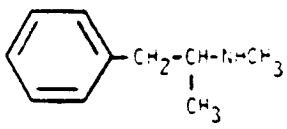
26. N-methylation of MDA yields MDMA which retains the psychotomimetic properties of MDA.

27. N-methylation of amphetamine yields methamphetamine which retains the central nervous system activity of amphetamine.

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

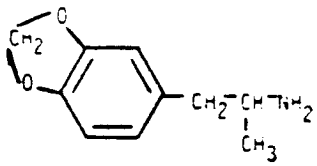


amphetamine

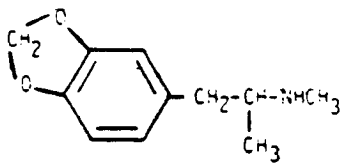


methamphetamine

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



MDA



MDMA

30. MDMA produces pharmacological effects in common with both central nervous system stimulants like amphetamine, and hallucinogens like MDA in animals.

31. MDA and MDMA both produce central nervous system stimulation as measured by increased locomotor activity in mice.

32. Tests conducted by Braun, Shulgin and Braun show that at an oral dose of 20 mg./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."

33. A study conducted by Intox Laboratories reported significantly reduced body weights at 7 and 14 days following initiation of MDMA dosing in rats.

34. The Intox Laboratory study also reported that rats who had been administered MDMA showed hyperactivity, excitability, aggressive behavior and stereotypic behavior.

35. 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 1½ 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.

36. 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 test showed that MDMA produces an increased analgesic effect over that produced by MDA.

37. MDA and MDMA both produce an increase in body temperature when administered to rabbits at similar potencies. Hyperthermia in rabbits is reported to be a measure of central nervous system activity. 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 believes that it is probably the best animal test at present for estimating psychotomimetic potency.

38. 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.

39. In mice, dogs and monkeys, MDA and MDMA produce the same spectrum of pharmacological effects when observed during toxicity studies. 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. These effects are part of what is described as the classical pharmacological response of the dog to intravenous mescaline.

40. The lethality of a compound is reported as an LD_{50}, which is the dose of a drug which will kill 50% of the animals treated with that dose.

41. The LD_{50}'s for mescaline, MDA and MDMA were determined by intravenous or intraperitoneal administration in five species of animals. MDMA had LD_{50}'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.

42. Intraperitoneal LD_{50}'s for MDA and MDMA were determined in mice by Dr. Davis. The LD_{50}'s of MDMA and MDA were substantially the same with the LD_{50} for MDA equalling 90.0 mg./kg. and the LD_{50} for MDMA equalling 106.5 mg./kg. Dr. Hardman found the LD_{50} of MDA to be 92 mg./kg. 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.

43. In the study conducted by Intox Laboratories the oral LD_{50} for MDMA in rats was estimated to be approximately 325 mg./kg. 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.

44. MDMA, MDA, amphetamine and methamphetamine produce neurotoxic effects when administered to animals. MDMA and MDA are neurotoxic in rats at doses which are very low compared to the neurotoxic doses of amphetamine and methamphetamine.

45. MDMA and MDA both produce long term reduction in serotonin levels and serotonin uptake sites in the rat brain. These neurochemical depletions are due to the destruction of serotonin nerve terminals as determined by visual staining techniques.

46. 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.

47. Although single injections of MDMA may be slightly less neurotoxic than MDA, MDMA, used chronically, appears to be more neurotoxic than MDA.

48. The neurotoxicity of amphetamine and methamphetamine has been determined in rats, guinea pigs and monkeys.

49. MDMA and MDA may produce the same neurotoxic effects to serotonergic nerves in humans.

50. 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 another substance. 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.

51. 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.

52. 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 that, at the tested doses, another type of pharmacological effect may predominate.

53. MDMA shares discriminative stimulus properties in common with amphetamine and MDA in drug discrimination studies in rats.

54. 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.

55. Rats trained to recognize MDA recognized MDMA in drug discrimination studies conducted by Dr. Glennon.

56. 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.

57. MDMA showed partial generalization (52% correct response) in rats trained to recognize DOM, at a specific dose.

58. 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 press a lever for intravenous delivery of a known drug reinforcer.

59. 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 cocaine.

60. 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.

61. Drs. Shulgin and Nichols first reported that MDMA produces psychotomimetic effects in man in 1976. These effects are described as intoxication, altered state of consciousness and sympathomimetic stimulation.

62. 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.

63. In a 1978 publication, Dr. Shulgin reported that racemic MDMA produced a high level of intoxication in man at doses of 100-160 mg. 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.

64. 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 160 mg. The effective dose of MDA was 80-120 mg., while that of MDMA was 100-160 mg. 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."

65. The Haight-Ashbury Free Medical Clinic in San Francisco treats approximately three to four 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 150 mg. each. The use of higher doses produces rapid pulse and heartbeat, severe anxiety, paranoia, fear, insomnia, psychological craving for the drug and depression.

66. 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 (200 mg.) produce effects similar to those of LSD. The high dose effects include hallucinations, either visual, tactile, olfactory or auditory.

67. 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.

68. 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.

69. 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 judgment, 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.

70. MDMA was first identified by a DEA laboratory in 1972. Between 1972 and April 1985, DEA laboratories identified 41 exhibits of MDMA consisting of over 60,000 dosage units.

71. 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.

72. MDMA is available in tablets, capsules and powders with recent analyses indicating approximately 110 mg. of racemic MDMA per dosage unit. MDMA has been encountered in many sections of the United States and other countries.

73. Since 1978, non-Federal forensic laboratories have reported over 41 exhibits of MDMA to DEA.

74. 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.

75. 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.

76. Pharm Chem reported 20 submissions of MDMA between May 1983 and May 1984, when it discontinued its testing service.

77. Toxicology Testing Service reported 19 submissions of MDMA between April 1984 and March 1985.

78. 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.

79. A DEA investigation conducted in June 1984 of a suspected cocaine distributor resulted in information concerning the widespread availability of "Ecstasy," or MDMA, in the Dallas, Texas area.

80. "Ecstasy," 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 110 mg. of MDMA.

81. 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; $70 per gram in New York; $85 per gram in California, and $10–$20 per dose in New Hampshire.

82. Dr. Inaba from the Haight-Ashbury 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.

83. 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.

84. Students at the University of Texas in Austin indicate that MDMA is easily available on campus at about $5 to $20 per tablet.

85. Dr. Ingrasci, a psychiatrist who has himself used MDMA on patients, 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.

86. Dr. Joseph J. Downing, a practicing psychiatrist in San Francisco, California, conducted a pilot study in 1984 into the effects in healthy humans of a single exposure to MDMA. The 21 subjects in Dr. Downing's MDMA study had all used MDMA previously. One had used MDMA 15 times, one 10 times, and one only once. The mean frequency of use of the 21 subjects was once every 2.2 months.

87. Dr. Lester Grinspoon reports that MDMA is being taken by a growing number of people, particularly students and young professionals in a casual and recreational manner.

88. Dr. George Greer, a practicing psychiatrist in Santa Fe, New Mexico, has used MDMA as an adjunct to psychotherapy in clinical work. He reported that one of his subjects, after taking the unusually high dosage of 350 mg. of MDMA, reported visual hallucinations, illusions, hearing impairment, brief memory loss and distortion in depth perception.

89. Between 1977 and 1981, the Drug Abuse Warning Network (DAWN) reported eight emergency room episodes associated with the use of MDMA.

90. MDMA is reported to have been associated with two overdose deaths. One death occurred in Seattle, Washington in 1979, and one in Santa Monica, California.

91. 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.

92. Therefore, the Administrator finds that MDMA has a high potential for abuse.

Discussion

The phrase "currently accepted medical use in treatment in the United States" is found in 21 U.S.C. 812(b). It is one of the three findings required for placement of a substance into one of the five Schedules of the Controlled Substances Act. Whereas placement of a drug or other substance into Schedules II through V requires a finding that the substance has a currently accepted medical use in treatment in the United States, placement of a substance into Schedule I requires a finding that the substance "has no currently accepted medical use in treatment in the United States." 21 U.S.C. 812(b)(1)(B). The Controlled Substances Act does not define this term.

The Administrator concludes that the term "currently accepted medical use in treatment in the United States" means that the drug or other substance is lawfully marketed in the United States pursuant to the Federal Food, Drug and Cosmetic Act of 1938 (FDCA), 21 U.S.C. 355. The FDCA establishes procedures regarding approval of drugs for marketing in the United States, and an exemption for investigational use of approved drugs prior to marketing. These procedures require that FDA must approve a new drug as being safe and effective before it may be introduced into interstate commerce in the United States.

If a substance is not marketed in interstate commerce in the United States, it is not manufactured by the pharmaceutical manufacturers who are licensed by the FDA to produce the vast array of medications currently available in this country; it is not distributed by pharmaceutical wholesalers licensed to sell pharmaceuticals, it is not stocked in retail pharmacies, hospitals and other medical facilities which daily dispense drugs to patients; and it cannot be prescribed by the hundreds of thousands of physicians and other practitioners who are authorized by their licenses and registrations to prescribe pharmaceuticals, including controlled substances, in the course of their professional practices. Such a substance cannot be said to have a "currently accepted medical use in *treatment* in the United States." (Emphasis added)

The complex system of approval for marketing and conditions for use of non-approved drugs for investigational purposes is designed 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." This interpretation is also consistent with that of the Uniform Controlled Substances Act, which has been adopted by almost all of the 50 states.

The Administrative Law Judge, in recommending that the Administrator find that MDMA has an accepted medical use in treatment, urged that the Administrator look at "what is actually going on within the health care community" in order to make this determination. The Administrator cannot accept this recommendation. The Administrator cannot, consistent with his responsibility to protect the American public from the abuse and misuse of dangerous drugs, declare legitimate a substance which has not been found safe and effective under the procedures required by the FDCA. He cannot find that a drug, which is not available through commercial, legitimate channels to the medical community, has an "accepted medical use in treatment in the United States." The fact that a handful of physicians are of the opinion that a substance may have therapeutic value is not an acceptable alternative to the thorough clinical and preclinical evaluation which precedes the approval of an NDA.

Another finding required to be made by the Administrator for placement of a substance in Schedule I is that "there is a lack of accepted safety for use of the drug or other substance under medical supervision." The same rationale discussed with regard to "accepted medical use" applies to "accepted safety for use . . . under medical supervision."

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."

Instead of relying on scientific data, or the opinion of the Food and Drug Administration, the Administrative Law Judge chose to rely upon the "world of health care practitioners" to determine "accepted safety for use." He chose to disregard scientific, controlled studies conducted by scientific researchers which have shown MDMA to be neurotoxic when administered to rats, and instead substituted the anecdotal judgments of a handful of physicians who observed the behavior of human animals under the influence of MDMA.

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 and evaluated by the FDA. These determinations are given great weight by the Administrator in evaluating scientific and medical matters.

For placement of a substance in Schedule I, the Administrator is also required to find that "the drug or other substance has a high potential for abuse."

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, both substances with an established high potential for abuse. 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.

The Administrator finds that the Agency sustained its burden that 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.

Because the Administrator has found that MDMA has no accepted medical use in treatment and has a high potential for abuse, it is unnecessary to address the issue of "whether a drug which has potential for abuse but no currently accepted medical use in treatment can lawfully be placed in any schedule other than Schedule I."

In reaching the conclusion that MDMA should be placed in Schedule I of the Controlled Substances Act, the Administrator has also considered the following information. In 1983, the World Health Organization recommended that MDMA be placed in Schedule I of the Convention on Psychotropic Substances (CPS), 1971, and the United Nations Commission on Narcotic Drugs subsequently placed MDMA in Schedule I.

In addition, MDMA is controlled in Schedule H of the Canadian Food and Drug Act, along with MDA and LSD. Reports of clandestine manufacture and distribution of MDMA continues in Canada. The Federal Republic of Germany has also reported the clandestine manufacture and distribution of MDMA.

The Administrator has read with interest the comments from various parties in the record concerning what effect placement of MDMA into Schedule I would have on legitimate research into the substance.

The Controlled Substances Act contains specific provisions for research with Schedule I substances. The registration provisions are found in 21 U.S.C. 823(f). 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.

The information required to be contained in this 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 a mechanism for researchers wishing to conduct clinical (human) investigations with controlled substances in Schedule I.

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." 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.

A review of the above regulations demonstrates that those who wish to conduct research with MDMA have available avenues by which to pursue such research.

Placement of a substance into Schedule I and designating it as a hallucinogenic imposes certain regulatory requirements on those handling the substance. Since MDMA has been a Schedule I controlled substance since July 1, 1985, the requirements imposed by the CSA and implementing regulations continue as follows:

1. *Registration.* Any person who manufactures, distributes, delivers, imports or exports MDMA, or who engages in research or conducts instructional activities with respect to this substance, or who proposes to engage in such activities, must be registered to conduct such activities in accordance with Parts 1301 and 1311 of Title 21 of the Code of Federal Regulations.

2. *Security.* MDMA must be manufactured, distributed and stored in accordance with §§ 1301.71 through 1301.76 of Title 21 of the Code of Federal Regulations.

3. *Labeling and Packaging.* All labels and labeling for commercial containers of MDMA must comply with the requirements of §§ 1302.03 through 1302.05, 1302.7 and 1302.08 of Title 21 of the Code of Federal Regulations.

4. *Quotas.* All persons required to obtain quotas for MDMA shall submit applications pursuant to §§ 1303.12 and 1303.22 of Title 21 of the Code of Federal Regulations.

5. *Inventory.* Every registrant required to keep records and who possesses any quantity of MDMA shall take an inventory pursuant to 1304.11 through1304.19 of Title 21 of the Code of Federal Regulations of all stocks of this substance on hand.

6. *Records.* All registrants required to keep records pursuant to 1304.21–1301.27 of Title 21 of the Code of Federal Regulations shall do so regarding MDMA.

7. *Reports.* All registrants required to submit reports pursuant to §§ 1304.37 through 1304.41 of Title 21 of the Code of Federal Regulations shall do so regarding MDMA.

8. *Order Forms.* All registrants involved in distribution of MDMA shall comply with the order form requirements of §§ 1305.01 through 1305.16 of Title 21 of the Code of Federal Regulations.

9. *Importation and Exportation.* All importation and exportation of MDMA shall be in compliance with Part 1312 of Title 21 of the Code of Federal Regulations.

10. *Criminal Liability.* Any activity with respect to MDMA not authorized by, or in violation of, the Controlled Substances Act or the Controlled Substances Import and Export Act continues to be unlawful. The criminal penalties are those of a Schedule I hallucinogenic.

Pursuant to 5 U.S.C. 605(b), the Administrator certifies that the placement of MDMA into Schedule I of the Controlled Substances Act will have no impact upon small businesses or other entities whose interests must be

considered under the Regulatory Flexibility Act (Pub. L. 96–354). This action involves the control of a substance with no currently approved medical use or manufacture in the United States.

In accordance with the provisions of section 201(a) of the Controlled Substances Act (21 U.S.C. 811(a)), this scheduling action is a formal rulemaking "on the record after opportunity for a hearing." Such proceedings are conducted pursuant to provisions of the Administrative Procedures Act, 5 U.S.C. 556 and 557, and as such have been exempted from the consultation requirements of Executive Order 12291 (46 FR 13193).

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Narcotics, Prescription drugs.

Under the authority vested in the Attorney General by section 201(a) of the Controlled Substances Act (21 U.S.C. 811(a)) and delegated to the Administrator of the Drug Enforcement Administration by regulations of the Department of Justice, 28 CFR 0.100(b), the Administrator hereby orders that Part 1308, Title 21, Code of Federal Regulations, be amended as follows:

PART 1308—SCHEDULES OF CONTROLLED SUBSTANCES [AMENDED]

1. The authority citation for Part 1308 continues to read as follows:

Authority: 21 U.S.C. 811, 812, 871(b).

2. Section 1308.11 is amended by redesignating the existing paragraphs (d)(7) through (d)(24) as (d)(8) through (d)(25) and adding a new paragraph (d)(7) as follows:

§ 1308.11 Schedule I.

* * * * *

(d) * * *

(7) 3,4-methylenedioxymethamphetamine (MDMA). . . . 7405

* * * * *

3. Section 1308.11 is amended by removing paragraph (g)(1) and redesignating the existing paragraphs (g)(2) through (g)(12) as (g)(1) through (g)(11).

* * * * *

Dated: October 8, 1986.

John C. Lawn,

Administrator.

[FR Doc. 86-23080 Filed 10-10-86; 8:45 am]

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UNITED STATES DEPARTMENT OF JUSTICE

Drug Enforcement Administration

In The Matter Of MDMA SCHEDULING	)	Docket No. 84-48

OPINION AND RECOMMENDED RULING, FINDINGS OF FACT, CONCLUSIONS OF LAW AND DECISION OF ADMINISTRATIVE LAW JUDGE

ON ISSUES TWO THROUGH SEVEN

FRANCIS L. YOUNG, Administrative Law Judge

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Dated: MAY 22 1986

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OPINION AND RECOMMENDED RULING, FINDINGS OF FACT, CONCLUSIONS OF LAW AND DECISION OF ADMINISTRATIVE LAW JUDGE

ON ISSUES TWO THROUGH SEVEN

I.

Introduction

This is a rulemaking proceeding pursuant to the Controlled Substances Act as amended[1] (the Act or the CSA) to determine in which schedule, if any, of the five schedules established by the Act, the substance 3, 4-methylene-dioxymethamphetamine, also known as MDMA, should be placed. The proceeding is being conducted pursuant to Subchapter II of Chapter 5 of Title 5, United States Code, the Administrative Procedure Act, after opportunity for a hearing.[2]

The Act itself placed a great many substances in one schedule or another. It vested the Attorney General with the authority, after considering several prescribed factors, to place other substances in appropriate schedules, to move substances from one schedule to another, and to de-schedule them. That authority has been delegated to the Administrator of the Drug Enforcement Administration (DEA).[3]

1 P.L. 91-513, 84 Stat. 1242, 21 U.S.C. §§ 801, et seq.

2 21 U.S.C. § 811(a).

3 28 C.F.R. § 0.100.

At the commencement of this proceeding in July 1984 MDMA was not listed in any schedule. At that time DEA published in the Federal Register[4] a notice of proposed rulemaking to place the substance in Schedule I. A number of persons filed comments and objections and requested a hearing. This administrative law judge was requested by the then-Deputy Administrator to preside and to provide the Administrator with a certified record and recommended findings of fact, conclusions of law and decision.

At a preliminary prehearing conference of participants on February 1, 1985 it was suggested that one of the issues identified presented a purely legal question which might be decided without the need of any evidence and in advance of the other issues in the case. (The Deputy Administrator had specified this issue as one on which a recommended conclusion was to be prepared for the Administrator.) After considering memoranda submitted by the participants the administrative law judge agreed and accepted the suggestion. The judge called for briefs from the parties on that issue. It was designated issue number 1, and was stated thus:

> 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 than Schedule I?

After studying the briefs the judge issued a recommended decision on that issue, dated June 1, 1985. He recommended, first, that the language of the Act was such that a substance with a potential for abuse less than a "high" potential, and having no currently accepted medical use in treatment, cannot be placed in <u>any</u> of the five schedules. (Clearly, a substance <u>with</u> a "high" abuse potential and no accepted medical use in treatment, must be placed in Schedule I.) Alternatively the judge recommended, based upon court decisions interpreting the Act, actions of the Congress, legislative history and DEA's own past

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4 49 F.R. 30210 (1984).

actions, that such a substance should be placed in either Schedule III, IV or V depending upon its degree of potential for abuse. In a letter to the administrative law judge dated October 7, 1985 the Administrator advised that he had decided not to issue a final agency ruling on that initial issue until he had received the entire record at the conclusion of the case.

Meanwhile, the proceeding continued with respect to the remaining issues. Direct examination testimony of all witnesses was submitted in written narrative form. Exhibits were identified and submitted. Hearing sessions for cross-examination of witnesses were held in Los Angeles, California, Kansas City, Missouri and Washington, D.C. on June 10, July 10 and 11, October 8, 9, 10 and 11 and November 1, 1985. The participants[5] submitted briefs and proposed findings and conclusions, and oral argument was heard in Washington, D.C. on February 14, 1986.[6]

The administrative law judge has carefully considered all the evidence of record and the arguments of the participants, as well as the written comments received during the comments period early on in the proceeding. He submits herein to the Administrator his recommended findings, conclusions and decision with respect to the issues other than Issue 1.

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5 The participants are the Agency staff (DEA or the Agency); George Greer, M.D., Lester Grinspoon, M.D., Thomas B. Roberts, Ph.D. and James Bakalar (Greer-Grinspoon); McNeilab, Inc. and Hoffmann-La Roche, Inc. (McNeilab); Lyn B. Ehrnstein, Esq., (Ehrnstein); and David E. Joranson (Joranson). See Memorandum to Counsel dated March 22, 1985.

6 There are ten volumes of transcript. The first contains the preliminary session on February 1, 1985. The remainder contain the testimony on cross examination and the oral argument. They have been numbered 1 through 10, and are cited herein as follows:

February 1, 1985	Tr 1	October 9, 1985	Tr 6
June 10, 1985	Tr 2	October 11, 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	February 14, 1986	Tr 10

II.

Recommended Ruling

The administrative law judge recommends that the proposed findings and conclusions submitted by the participants be rejected by the Administrator, except to the extent they are included in the judge's recommendations, for the reason that they are irrelevant, unduly repetitious or not supported by substantial evidence. The judge's recommended findings and conclusions are contained in the text of this opinion.

III.

Issues

The issues yet to be disposed of are as follows:

> 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 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 [including issue 1], MDMA can lawfully be scheduled in a schedule other than Schedule I, in which schedule should it be placed?

IV

"Currently Accepted Medical Use
In Treatment In The United States"

Introduction

Section 812(b) of Title 21 U.S.C. provides that, aside from actions mandated by certain international agreements, which are not applicable here, and except in the case of an immediate precursor, with which we are not concerned, "a drug or other substance may not be placed in any schedule unless the findings required for such schedule are made with respect to such drug or other substance." It is the responsibility of the Administrator of DEA to make these findings after receiving an evaluation and recommendation from the Secretary of the Department of Health and Human Services (HHS)[7] pursuant to § 811(b). After making his findings, the Administrator is to place the drug or substance in question in the appropriate schedule of the five schedules established by the Act.

The findings required for placement in each schedule are set out in Section 812(b) as follows:

> (1) 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.
>
> (2) Schedule II.-
>
> (A) The drug or other substance has a high potential for abuse.

7 The Secretary's input into the matter comes to the Administrator from the Assistant Secretary of Health, HHS.

(B) The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions.

(C) Abuse of the drug or other substances may lead to severe psychological or physical dependence.

(3) Schedule III.-

(A) The drug or other substance has a potention for abuse less than the drugs or other substances in schedules I and II.

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

(C) Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.

(4) Schedule IV.-

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

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

(C) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule III.

(5) Schedule V.-

(A) The drug or other substance has a low potential for abuse relative to the drugs or other substances in schedule IV.

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

(C) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule IV.

(Emphasis added).

Thus a finding must be made for each drug or other substance to be

scheduled as to whether or not it has a "currently accepted medical use in treatment in the United States".

What constitutes such use? What does this phrase mean? How is the Administrator to ascertain whether or not a drug has a currently accepted medical use in treatment in this country? This is essentially a legal issue of statutory interpretation. No findings of fact are called for.

To the Agency staff the answer is simple. They assert that "accepted medical use" means approval by the Food and Drug Administration (FDA) of HHS pursuant to the procedures established by Section 505 of the Federal Food, Drug and Cosmetic Act of 1938 (FDCA), 21 U.S.C. § 355. DEA need only ask FDA whether the drug or substance in question has received FDA approval under the FDCA in order to ascertain the existence, vel non, of "accepted medical use".

There is no denying that such a situation would greatly simplify the scheduling task of the DEA staff. It provides a quick solution to the problem for DEA. It provides a certain answer. But it is wrong.

The FDCA

The FDCA was enacted in 1938. It established procedures which a person must follow, and approvals he must obtain, before he may "introduce or deliver for introduction into interstate commerce any new drug". 21 U.S.C. § 355(a). In a word the FDCA, as amended, requires that FDA must approve a new drug as being safe and as being effective for a stated purpose - before it may be introduced into interstate commerce in the United States. There is nothing in that statute authorizing FDA to approve a new drug for use in the practice of

medicine by a licensed physician. The power to grant or withhold such approval would constitute regulation of the practice of medicine. The FDCA does not empower the FDA to do this. The FDA itself has repeatedly stated that it is not empowered to attempt such regulation.

The question of FDA's authority in this regard has arisen when that agency has considered the practice of physicians using marketed drugs for purposes which the FDA has not approved.[8] In 1972, FDA summed up its view on this subject when, in the preamble to a proposed rule on drug labeling, it stated:

> If an approved new drug is shipped in interstate commerce with the approved package insert and neither the shipper nor the recipient intends it be used for an unapproved purpose, the requirements of section 505 of the Act are satisfied.
>
> Once the 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 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

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8 Under the FDCA, the labeling of any prescription drug, whether subject to approval or not, must be adequate for the drug's intended purposes. In the case of prescription drugs (as opposed to "over-the-counter" drugs available without a prescription), the requirements are met by conditioning availability on a practitioner's prescription, and on there being labeling directions for physicians and pharmacists (as opposed to laymen) as to the prescribing, dispensing, and administration of the drug. 21 C.F.R. § 201.100.

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.

37 Fed. Reg. 16503 (1972).

Subsequently, in 1975, five years after enactment of the Controlled Substances Act, the Food and Drug Administration wrote as follows:

> The comments recommended that the proposed regulations be revised to require an appropriate statement in package inserts that, in addition to the conditions of use which the manufacturer may recommend to physicians in compliance with the law and Food and Drug Administration regulations, there are other conditions of use for which the drug may be regarded as safe and effective on the basis of the experience of critical physicians using the drug in the practice of medicine over a period of years.
>
> The Commissioner stated in a separate notice of proposed rulemaking published in the Federal Register of August 15, 1972 (37 Fed. Reg. 16503)[9], concerning the use of a drug for conditions not included in its labeling, that the labeling does not intend either to preclude the physician's use of his best judgment in the interest of the patient or to impose liability if he does not follow the package insert. The Commissioner clearly recognizes that the labeling of a marketed drug does not always contain all the most current information available to physicians relating to the proper use of the drug in good medical practice. Advances in medical knowledge and practice inevitably precede the labeling revision by the manufacturer and formal labeling approval by the Food and Drug Administration. Good medical practice and patient interest thus require that physicians be free to use drugs according to their best knowledge and judgment. Certainly where a physician uses a drug for a use not in the approved labeling, he has the responsibility to be well informed about the drug and to base such use on a firm scientific rationale or on sound medical evidence, and to maintain

9 Quoted immediately above.

> adequate medical records of the drug's use and effects, but such usage in the practice of medicine is not in violation of the Federal Food, Drug and Cosmetic Act.

40 Fed. Reg. 15393-94 (1975) (emphasis added).

In 1979, the Food and Drug Administration once more reiterated this view:

> Good medical practice and patient welfare require that physicians remain free to use drugs according to their best knowledge and judgment . . . .

44 Fed. Reg. 37435-36 (1979).

Once again, in June 1983, the FDA repeated its view that it does not have the authority to regulate the practice of medicine:

> Although no final rule has been issued on this subject, the Agency has continued to apply the principle set forth in the preamble to the 1972 proposal. In FDA's Drug Bulletin of April 1982, the Agency sought to clarify and reiterate the position that the Act does not regulate the "practice of medicine." Once a drug product has been approved for marketing, a physician may, in treating patients, prescribe the drug for use not included in the drug's approved labeling. The primary legal constraints in that situation are State laws on medical practice and products liability law. The IND Rewrite proposal would codify the Agency's longstanding position that the regulations do not apply to the "practice of medicine," though the proposal does not purport to define with specificity such practice in terms of the Act.

48 Fed. Reg. 2673 (June 9, 1983).

Finally, the Food and Drug Administration reemphasized this position in a filing with the United States Court of Appeals for the District of Columbia Circuit in 1983. In the course of its argument in the 1983 case, the FDA emphasized the

> commonly recognized exception to the Act's broad and protective coverage: the 'practice-of-medicine' exemption. FDCA's legislative history expresses a specific intent to prohibit FDA from regulating physicians' practice of medicine. According to the Commissioner, FDCA does not regulate physicians in their practice because physicians are licensed by the states. Letter from the Commissioner at 3, JA 88.

Chaney v. Heckler, 718 F.2d 1174, 1179 (D.C. Cir. 1983), rev'd, _____ U.S. _____, 84 L. Ed. 714 (1985). (Footnotes omitted).

A word of caution is called for. In the penultimate quotation above, the phrase "approved for marketing" appears. This term is frequently used as a substitute for the statutory language "introduced into interstate commerce". Agency counsel slipped into this inaccuracy in oral argument on February 14, 1986. (Tr 10, p.6) It is important to keep clearly in mind what Congress was doing when it enacted the FDCA in 1938 - it was regulating the interstate commerce of substances. It was not undertaking to define the acceptable practice of medicine. It was not attempting to provide a yardstick for "accepted medical use".

The above-quoted statements by the FDA, which carries out the provisions of the FDCA, provide no basis for turning to that statute for a determination of what does or does not constitute "accepted medical use". Indeed, the FDA's own pronouncements are clearly to the contrary.

DEA's brief in this proceeding points to another statement by FDA, in 1982, prompted by efforts to "legalize" marihuana. In its published proposed recommendations to DEA on the scheduling status of that substance and its components, FDA said, referring to the language of § 812(b):

> 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)

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.

He 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 the NDA, the agency has no basis for concluding that medical use of the drug in treatment can be considered acceptable by medical standards.

The last quotation flies directly in the face of the preceding statements of statutory interpretation by FDA, issued over a period of eleven years. It represents a complete reversal of position with no stated basis whatsoever. One can only conclude that, in the context of the battle over marihuana, FDA temporarily lost sight of its long-acknowledged lack of statutory authority to regulate the practice of medicine. Perhaps it failed to realize the full effect of its statement. FDA is not charged with forming a conclusion, binding on the medical profession, "that medical use of the drug in treatment can be considered acceptable by medical standards." FDA is to pass on the safety and efficacy of a drug simply and solely in connection with approving it for "introduction into interstate commerce."

FDA is acting properly if it attempts to ascertain whether or not the medical profession has accepted use of a drug in treatment as the agency determines whether or not to allow the drug's introduction into interstate commerce. Acceptance of use in treatment, with other factors, is certainly an appropriate consideration. But nowhere in either statute, the FDCA or the CSA, is it provided that FDA's fiat will be binding on the medical profession with respect to what is, or is not, accepted medical practice or accepted medical use.

There can be a very simple reason why there exists no NDA for a particular drug and why FDA has not approved it for introduction into interstate commerce: no one may have sought such approval from FDA. The fact no one has sought approval does not necessarily mean that no one is using the drug and that such use is not accepted by the profession. There are very real economic factors affecting whether an NDA is sought for a drug.

The Controlled Substances Act

The Controlled Substances Act (CSA) was enacted in 1970, 32 years after the Food, Drug and Cosmetic Act. In 1970 the Congress was well aware of its 1938 handiwork. There are several specific references to the 1938 statute in the 1970 enactment. Thus we find in the CSA that "drug" is defined by specific reference to a section of the FDCA; see 21 U.S.C. § 802(12). Congress excluded from the Attorney General's scheduling power any substance permitted by the FDCA to be sold "over the counter and without a prescription"; see 21 U.S.C. § 811(g)(1). Congress specifically referred to the investigational new drug provisions of the FDCA in the CSA; see 21 U.S.C. §§ 827(c)(2)(A), 827(f). Other references to provisions of the FDCA are found in the CSA at 21 U.S.C. §§ 825(a), 825(b), 829(a) and 829(d). Congress could easily have linked the phrase "accepted medical use in treatment" in the CSA to some provision of the FDCA, and FDA's authority thereunder, had it desired to do so. It did not do so.

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The Agency's reply brief[10] refers to the "somewhat sparse legislative history of the Controlled Substances Act relating to 'accepted medical use'." No participant quotes any comment on the meaning of this phrase from a committee report or floor manager. However, there were references to the phrase in the testimony of several witnesses.

Dr. John Jennings, then Acting Director of the Bureau of Drugs, FDA, testified as follows at one point:

> Q: Let me ask one question: when a drug is under investigation pursuant to investigational new drug applications, is the drug considered to have an accepted medical use?
>
> Dr. Jennings: Usually not, although it might.
>
> Q: Could you enlarge on that?
>
> Dr. Jennings: Yes, sir. The exemption for investigational use is usually granted for a drug for which the medical use has not been established so in most cases that would be so, there would not be an accepted medical use.
>
> However, drugs that have one or maybe several accepted medical uses might be under investigation for additional medical uses.
>
> Q: But in the great majority of cases —
>
> Dr. Jennings: It would be true that the accepted medical use would not have been established.

House Hearings, at 343 (emphasis added).

The subject came up also during the testimony of Michael R. Sonnenreich, Deputy Chief Counsel of the Bureau of Narcotics and Dangerous Drugs (BNDD), DEA's predecessor agency, of John Ingersoll, Director of BNDD, and of Dr. Roger Egeberg, Assistant Secretary of HEW. They testified as follows:

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10 Government's Response To The Findings, etc., Submitted by Drs. Greer and Grinspoon, et al., etc., p. 13.

Mr. Sonnenreich: [Criterion] Two [no accepted medical use] is a factual determination and normally where we get such information is through the AMA or WHO. You don't have to be a doctor to find out whether or not it has an accepted medical use in the United States or not. So the fact that you are asking whether it has got accepted medical use is something that a lawyer can find out as well as a doctor.

House Hearings, at 165 (emphasis added).

Mr. Rogers: Under Schedule I drugs. Would HEW or the Department of Justice be able to determine on a drug a lack of accepted safety for use under medical supervision?

Dr. Egeberg: I would think that HEW would expect to have a good deal to say on that.

Mr. Rogers: All right. HEW would have the competence there. I think this would be admitted. What about no accepted medical use in the United States?

Dr. Egeberg: Well, I would think that HEW would be the primary source, through its various agencies and its contacts, for information on that subject.

House Hearings, at 194 (emphasis added).

Mr. Ingersoll: I must also point out that this review [prior to registration of researchers by the Department of Justice] is only required for Schedule I substances which the medical profession has already determined have no legitimate medical use in the United States.

House Hearings, at 678 (emphasis added).

Mr. Rogers: So the only category of [Schedule] I is simply for research?

Mr. Sonnenreich: Yes, sir, and that is because they have no medical use as determined by the medical community.

House Hearings, at 696 (emphasis added).

Mr. Sonnenreich: Mainly, our feeling is that the trigger on your Schedule I drugs which are really different from your II, III and IV drugs. It is this basic determination that is not made by any part of the federal government. It is made by the medical community as to whether or not the drug has medical use or doesn't.

Mr. Rogers: If it has medical use, Food and Drug probably would have authorized it, wouldn't they?

Mr. Sonnenreich: I assume so, sir.

House Hearings, at 718 (emphasis added).

From the foregoing exchanges it clearly appears that the spokesmen for BNDD and FDA were of the view in 1970 that one should turn to "the medical community" to ascertain the existence of accepted medical use in treatment, and that "a lawyer can find out as well as a doctor" whether such acceptance exists, and that "this basic determination is not made by any part of the federal government".[11]

This interpretation, provided to the Congress by Administration witnesses, contemporaneously with enactment, is reasonable and authoritative. The Congress has given no indication of having rejected it or of adopting another. It is in accord with the plain meaning of the language in the statute. The Congress had every opportunity to tie "accepted medical use" to FDA actions under the FDCA. It did not do so. The only rational conclusion is that it did not intend to do so.

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11 In their Reply Brief, at page 16, Agency counsel quote a sentence from a written statement submitted to the Congress on another occasion by Director Ingersoll in justification of the Schedule I placement of a particular substance. This one, isolated sentence appears directly to contradict Mr. Ingersoll's oral testimony to the Committee quoted above. To that extent it is inconsistent also with the quoted oral statements of Mr. Sonnenreich, Mr. Ingersoll's deputy chief counsel. In the circumstances, and being uninformed as to the full context of the written sentence, it would seem that the oral statements, made when the phrase was being specifically discussed, should be accepted as accurately expressing BNDD's opinion on the point. The only alternative is to conclude that Mr. Ingersoll was not a reliable witness at all and that none of his statements can be accepted.

Court Decisions

Court decisions have agreed with the FDA itself, and the BNDD spokesmen in 1970, that the FDA is not empowered to decree what is or is not proper medical practice.

> Congress did not intend the Food and Drug Administration to interfere with medical practice as between the physician and the patient. Congress recognized the 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. . . . Congressional intent set out in 37 Fed. Reg. 16503 (1972) indicates the Congress did not intend the Food and Drug Administration to interfere with medical practice and that the bill did not purport to regulate the practice of medicine as between the physician and the patient.
>
> * * *
>
> ". . . the physician can ascertain from medical literature and from medical meetings new and interesting proposed uses for drugs marketed under package inserts not including the new proposed usages . . . New uses for drugs are often discovered, reported in medical journals and at medical meetings, and subsequently may be widely used by the medical profession. . . . The manufacturer may not have sufficient commercial interests or financial wherewithal to warrant following the necessary procedures to obtain FDA approval for the additional use of the drug. When physicians go beyond the directions given in the package insert it does not mean they are acting illegally or unethically and Congress does not intend to empower the FDA to interfere with medical practice by limiting the ability of physicians to prescribe according to their best judgment.

United States v. Evers, 453 F. Supp. 1141, 1149, 1150 (M.D. Ala. 1978), aff'd 643 F.2d 1043 (5th Cir. 1981). (Emphasis added.)

In its opinion affirming the District Court in Evers, the Fifth Circuit observed:

> ***[T]he [FDCA] was intended to regulate the distribution of drugs in interstate commerce, not to restrain physicians from public advocacy of medical opinions not shared by the FDA.

United States v. Evers, 643 F.2d 1043, 1053, n. (1981).

Agency counsel's quote from the Fifth Circuit opinion in Evers (Reply Brief, p. 9) simply expresses recognition of the FDA's lack of power to regulate medical practice with reference to the specific facts of that case which centered on the use of a non-prescription drug for a purpose other than that stated in the package insert. The quotation in no way detracts from the court's recognition of the basic principle. It reinforces it.

Uniform Controlled Substances Act

The plebiscite conducted by participant Joranson of state regulatory officials is wholly irrelevant and immaterial. He asked them to express their interpretations, as regulators, of language in the Uniform Controlled Substances Act, not the language in the Federal statute with which we are concerned. It is the medical community which is to be consulted on the Federal statutory question, not state regulators working with different statutes.

Classification Of Alphacetylmethadol

The Agency's discussion of Congress' treatment of alphacetylmethadol has no relevance here. The Agency submitted a statement to the Congress about that substance, that "since the current use of alphacetylmethadol is limited to research, it has no currently accepted medical use. . . ." Whatever else was said about that substance was surplusage with respect to its accepted medical use.

Congressional Rescheduling of Methaqualone

In 1984 Congress enacted special legislation effectively placing the substance methaqualone in Schedule I.[12] Agency counsel now point to one sentence in a House Report concerning that legislation as evidencing an understanding by the Congress that "accepted medical use in treatment" was equated by the Committee with FDA "approval". Counsel's reliance on the quoted statement is misplaced.

To begin with, the statement is wrong. The Committee Report says: "[T]he 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". There is no such bar in the CSA. The CSA does provide, in 21 U.S.C. § 811(b) that "if the Secretary recommends that a drug or other substance not be controlled, the Attorney General shall not control the drug or other substance". But there is no language having the effect of the quoted statement in the House Report.

The very next sentence in the House Report, not quoted in the Agency's brief, is correct and does show the necessity for Congressional action to outlaw methaqualone at that time. The sentence says:

> The statutory findings required for agency scheduling decisions clearly state that the agency may not, in the absence of Congressional action, subject drugs with a currently accepted medical use in the United States to Schedule I controls.

The Report continues:

> There are circumstances when public health considerations require the Congress to exercise its responsibility to determine whether the adverse health effects caused by diversion of a drug outweigh its therapeutic usefulness and therefore warrant impositions of Schedule I controls.

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12 P.L. 98-329, 98 Stat 280, June 29, 1984. See Appendix.

> . . . Although methaqualone currently has an accepted medical use, there is a consensus of medical opinion that it has no unique therapeutic advantages over other available drugs and has a significantly higher incidence of and potential for abuse.
>
> * * *
>
> Should future research discover a new use for methaqualone or if it can be clinically demonstrated that methaqualone possesses therapeutic advantages not possessed by other sedative-hypnotic drugs, the Controlled Substances Act specifies procedures for administratively removing the drug from Schedule I and placing it in an appropriate schedule of the Act.[13]

The House committee was not focusing on the problem which concerns us at the moment. But implicit in the above language is recognition that what the medical profession is actually doing is not to be equated with an approval action by the FDA. Indeed, the Report shows that the Committee listened to the medical community. At least one physician is quoted in the Report, as is a report adopted by the House of Delegates of the American Medical Association.

The Agency brief states, p. 20:

> *** 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".

Counsel are mistaken. A careful reading of the statute enacted reveals that the Attorney General was directed to transfer the substance from Schedule II to Schedule I <u>first</u>, and <u>thirty days thereafter</u> the Secretary (FDA) is directed to withdraw the NDA. See Appendix.

Clearly, Congress was exercising its prerogative, which only it possesses, to enact legislation. DEA and FDA must operate within the procedural scheme

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

established for them by the Congress, but Congress is not so constrained. Congress, as it has the power to do, directed DEA to outlaw methaqualone regardless of the fact that it had an accepted medical use and regardless of the fact that the NDA had not yet been withdrawn by FDA.

Conclusion

The administrative law judge concludes that "accepted medical use in treatment in the United States" is not determined by NDA approvals or dis-approvals by FDA. It is determined, rather, by what is actually going on within the health care community.

V.

"Currently Accepted Medical Use"
Of MDMA

Let us, then, in the words of Deputy Chief Counsel Sonnenreich, consult "the medical community as to whether or not [MDMA] has medical use or doesn't." In this instance, as in many others, it is instructive for this tribunal to look to the courts for guidance.

Most court decisions are dealing with suits for medical malpractice. But the basic inquiry is the same as that in which we are presently engaged. Was the doctor's action acceptable, or is he to be considered culpable for taking it? How large a segment of the medical community must accept a mode of treatment before the courts will accept it and find no culpability in the doctor following it?

In Hood v. Philips, 537 S.W. 2d 291 (1976) the Texas Court of Civil Appeals found itself dealing with a claim of medical malpractice arising from a surgical procedure claimed to have been unnecessary. The court noted that the usual treatment for emphysema by the majority of the medical profession is non-surgical. The defendant doctor, however, resorted to surgery. The court said:

> ***This is a highly controversial procedure, but there is evidence that carotid body surgery is performed by at least one other doctor in Texas, a doctor in Boston, Massachusetts, and doctors in Japan, Poland and Italy. Until his retirement in 1967, defendant was apparently the only physician in the Houston area who employed this procedure. The defendant stated that eighty-five percent of some 1,200 persons on whom he has operated derived some benefit, but there is medical evidence in the record that the procedure is generally recognized as having no value in treating emphysema and in some cases may be detrimental to the patient's health.

537 S.W. 2d at 292. Noting that some courts had adopted a rule of "generally recognized treatment", the Texas court observed that courts have also enunciated a corollary to the rule that one should follow the better method, viz.:

> where there are several possible methods of treatment, a doctor will not be liable for a patient's injuries as long as the treatment is one followed by a respectable minority of the medical profession and his care under that treatment conforms with the general practice of reasonable physicians utilizing the same treatment.

Ibid. at 293. The Texas court quoted from an Arizona court decision, holding that

> a method of treatment, as espoused and used by . . . a respectable minority of physicians in the United States, cannot be said to be an inappropriate method of treatment or to be malpractice as a matter of law even though it has not been accepted as a proper method of treatment by the medical profession generally.

Ibid. at 294. Noting that the Federal District court in the Arizona case found a "respectable minority" composed of sixty-five physicians throughout the United States, the Texas court adopted as "the better rule" to apply in its case, that

> a physician is not guilty of malpractice where the method of treatment used is supported by a respectable minority of physicians.

. . . .

Ibid. The court sent the case back to the trial court for a determination applying that rule. One judge dissented, believing that the evidence in the particular case was insufficient to raise an issue of malpractice for the jury. He observed:

> . . . I fear the long term effect [will] discourage new procedures and techniques, so necessary to improve health care.

Ibid. at 297.

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In Chumbler v. McClure, 505 F.2d 489 (6th Cir. 1974) the Federal courts were dealing with a medical malpractice case under their diversity jurisdiction, applying Tennessee law. The Court of Appeals said:

> . . .The most favorable interpretation that may be placed on the testimony adduced at trial below is that there is a division of opinion in the medical profession regarding the use of Premarin in the treatment of cerebral vascular insufficiency, and that Dr. McClure was alone among neurosurgeons in Nashville in using such therapy. The test for malpractice and for community standards is not to be determined solely by a plebiscite. Where two or more schools of thought exist among competent members of the medical profession concerning proper medical treatment for a given ailment, each of which is supported by responsible medical authority, it is not malpractice to be among the minority in a given city who follow one of the accepted schools.

505 F.2d at 492. (Emphasis added).

How do we ascertain whether there exists a school of thought supported by responsible medical authority, and thus accepted? We listen to the physicians.

> The court and jury must have a standard measure which they are to use in measuring the acts of a doctor to determine whether he exercised a reasonable degree of care and skill; they are not permitted to set up and use any arbitrary or artificial standard of measurement that the jury may wish to apply. The proper standard of measurement is to be established by testimony of physicians, for it is a medical question.

Hayes v. Brown, 133 S.E. 2d. 102(Ga., 1963) at 105.

The courts and former Deputy Chief Counsel Sonnenreich are in accord.

Findings Of Fact

There is testimony in this record from reputable physicians, i.e., responsible medical authorities who constitute a respectable minority, that the use of MDMA is acceptable in the treatment of certain kinds of patients.

Dr. George Greer is a psychiatrist in private practice in New Mexico. He is Board Certified. He is also a part-time consultant psychiatrist at the penitentiary in New Mexico where he treats inmates. Prior to July 1, 1985 Dr. Greer had been doing clinical work with MDMA for four and one-half years. He had administered it to 76 patients. He found MDMA to be helpful as an adjunct to psychotherapy in certain cases. He considers himself a clinician, not a researcher. He has studied extensively in the field of using altered states of consciousness to facilitate psychotherapy and personal development.

In January 1983 Dr. Greer learned that MDMA was being used recreationally. He became concerned that its legitimate medical use might be challenged, so he wrote a paper describing his work with the substance. In this paper Dr. Greer intended simply to present the results of his experience using MDMA with patients. It was not his intention there to report on a formal, controlled testing program for MDMA to present a convincing argument definitely establishing the efficacy of MDMA. He believes that MDMA should be scheduled and subjected to some controls by DEA. He desires to see it placed in Schedule III. He desires to see formal research undertaken with the drug and funding made available for such research. He has informally sought such funding from at least two pharmaceutical companies, but they were not interested. The drug cannot be patented. He made informal contact with officials at FDA, suggesting that FDA provide funding for studies and promote research in the use of the drug. So far no one has made such funding available.

Dr. Rick J. Strassman is Assistant Professor of Psychiatry, University of New Mexico School of Medicine, in Albuquerque. He is medical director and principal investigator of a program in which marihuana or THC is being used to combat cancer chemotherapy-induced nausea and vomiting. This project is funded by the State of New Mexico with approval of FDA and the National Institute of Drug Abuse (NIDA). Previously he was Assistant Professor of Psychiatry at the University of California, Davis Medical Center. He has served as a psychiatrist at mental health centers in California and Alaska. He is board certified by the American Board of Psychiatry and Neurology.

Dr. Strassman is a member of the peer review committee which had been overseeing Dr. Greer's work with MDMA. Dr. Strassman testified:

> As a member of [Dr. Greer's] peer review board in New Mexico, I have reviewed his inclusionary and exclusionary criteria for entrance into the protocol, informed consent forms, protocol for administration of MDMA . . . ., the setting in which sessions occur, his results of follow-up, etc. In my opinion, he has included appropriate safeguards and has not experienced significant adverse reactions to this form of treatment, and that all individuals have experienced significant benefit. Therefore, within the standards of practice set forth by the physicians' community, MDMA has a currently accepted medical use in the hands of a qualified clinician (e.g., Dr. Greer).

Strassman Rebuttal Testimony, at 1-2.

Dr. Rodney A. Houghton was another member of Dr. Greer's peer review committee. He is a former Chief Resident in the Department of Psychiatry at the University of New Mexico and has conducted psychiatric clinics in four rural New Mexico counties. In this connection among other things he provided in-service training on various aspects of clinical psychiatry for law enforcement agencies including policemen, jailors and local sheriffs. He has served as an expert on

psychiatric care to the New Mexico State Department of Health and Environment concerning the State Mental Health Programs. As a psychiatrist he has been medical consultant to the Social Security Administration, HHS, reviewing psychiatric disability cases for the Disability Determination Unit of New Mexico. He has served as a member of the committee reporting to the State agency responsible for funding and maintaining standards for community mental health programs. He is a Clinical Assistant Professor of the University of New Mexico Department of Psychiatry. He is a member of the medical staffs of two psychiatric hospitals in Albuquerque. Dr. Houghton is in contact with and has worked with psychiatrists and other mental health care professionals throughout New Mexico. Dr. Houghton testified in this proceeding as follows:

> In summary, during the nine years of practicing psychiatry in New Mexico, I have become well acquainted with the academic community, rural and private practice standards of psychiatric evaluation and treatment. I have been involved at all levels of developing and maintaining quality medical treatment of psychiatric patients in this state -- in the political and government agency area, in the grassroots community level, and in the private profit and not-for-profit hospitals.
>
> * * *
>
> In my expert opinion, as one who is familiar with the accepted standards of psychiatric practice in New Mexico, indeed, having established many of those standards for five rural communities and community programs throughout the state, I believe Dr. Greer's use of MDMA is an accepted and safe medical practice. I base this opinion not only on my own experience and what I believe to be

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> acceptable, but also on my conversations with teachers and colleagues about his work.

Houghton Rebuttal Testimony, at 3-5.

Dr. Will L. MacHendrie was another member of Dr. Greer's peer review committee. In his testimony in this proceeding, given in April 1985, Dr. MacHendrie said:

> I am a Board Certified psychiatrist and for the past five years I have been working in community mental health and private practice in New Mexico.
>
> For the past two and one-half years, I have been on the Peer Review Committee for Dr. George Greer's use of MDMA. In that capacity, I have extensively reviewed his methodology and his results regarding therapeutic use of MDMA. I feel that there is definitely a medically accepted use of this drug in treatment, and that there is acceptable safety for use under medical supervision.

MacHendrie Rebuttal Testimony, at 1.

Dr. MacHendrie has served as Assistant Clinical Professor of Psychiatry at the University of California, Davis, and as Staff Psychiatrist for Sangre de Cristo Mental Health Service in New Mexico. He is now in private practice in Santa Fe.

Neither Dr. MacHendrie nor Dr. Houghton appears to have used MDMA in his treatment of patients. However, three California psychiatrists have done so. Dr. Philip Wolfson and Dr. Joseph Downing are in private practice in San Francisco. Each has used MDMA as an adjunct to therapy with certain patients. Each of them considers it to be an accepted medical use to do so.

Dr. Robert DuBois Lynch is a psychiatrist in private practice in La Jolla, California. He is also statewide psychiatric consultant to the Department of Rehabilitation of the State of California. He has not used MDMA in his practice although he would like to conduct research with it. He believes that in the area in which he lives, and in California generally, a psychiatrist using

MDMA for particular therapeutic purposes would be considered to be doing pioneering good medical practice by his colleagues.

This testimony, of course, as with the testimony of many of the witnesses, was given before the temporary Schedule I placement of MDMA on July 1, 1985 and is to be read in that context.

Four additional psychiatrists testified in these proceedings that, before its being placed in Schedule I on July 1, 1985, MDMA had a currently accepted medical use in psychotherapy for certain purposes and under certain conditions. They were Dr. Morris Lipton, professor of psychiatry at the University of North Carolina, Chapel Hill, and Deputy Editor of the American Journal of Psychiatry of the American Psychiatric Association; Dr. Norman Zinberg, clinical professor of psychiatry, Harvard Medical School; Dr. Lance Wright, practicing psychiatrist and Assistant Clinical Professor of Psychiatry, University of Pennsylvania and Associate Professor of Child Psychiatry, Hahnemann Medical College; and Dr. Richard Ingrasci, a psychiatrist in private practice in Watertown, Massachusetts.

No testimony to the contrary by any witness is brought to the attention of the administrative law judge by the Agency or any other participant.

Conclusion

The administrative law judge finds and concludes that, prior to its being proscribed effective July 1, 1985, MDMA did have "a currently accepted medical use in treatment in the United States." It is not presently being used in treatment because it has been proscribed.

VI

"Accepted Safety For Use"
Of MDMA

Section 812(b)(1) provides that, in order to place a substance in Schedule I, the Administrator is "required" to find that, with respect to the substance, "[t]here is a lack of accepted safety for use . . . under medical supervision." Stated issues numbered 3. and 6. in this proceeding are as follows:

> 3. What constitutes "accepted safety for use . . . under medical supervision" 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)?

These issues will now be considered.

The Agency staff takes the same position with respect to "accepted safety for use" generally, i.e., issue 3., as it took with respect to "accepted medical use in treatment." It asserts that "accepted safety for use" under the CSA is to be equated with approval by FDA under a different statute, the FDCA, as safe and effective, pursuant to 21 U.S.C. § 355(d). The appeal of this position, as providing a clear basis for a ruling with minimum effort to ascertain it, is as readily apparent here as it was with respect to "accepted medical use in treatment". This position cannot be accepted here for the same reasons that it cannot be accepted there:

- There is no basis in the text of the CSA for the Agency's position.

- Had the Congress intended this interpretation, it could easily have so provided in the CSA. It specifically referred back to

the previously enacted FDCA in other sections of the CSA, but it did do so here. This can only mean that Congress did not here intend to refer back.

- There is nothing in the legislative history to this effect.

- The only comment in testimony before Congress on this issue brought to light by the parties is the exchange between Congressman Rogers and FDA's Dr. Egeberg, quoted above on page 16.

It is to be noted that Dr. Egeberg did not say that the question of "accepted safety" for CSA purposes would be bindingly determined by FDA, utilizing the authority granted FDA 38 years earlier for FDCA purposes. The Assistant Secretary said that he "would think that HEW would expect to have a good deal to say on that". (Emphasis added.) Assuredly so. One would hope and expect FDA to have an informed opinion on the question, and make it available to DEA's Administrator for consideration together with all the other evidence received on the record after opportunity for a hearing. But the determinative "findings prescribed by subsection (b) of section 812", including accepted safety for use vel non, are to be made by the Administrator of DEA and by no one else. The statutory language is perfectly clear. 21 U.S.C. § 811(a)

The impossible situation to which the Agency position here would bring us is well pointed up by proposed finding number 6. on page 28 of its brief: "There is no legitimate commercial manufacturer of MDMA in the United States". If this is the criterion, "accepted safety" for use by physicians is reduced to

being determined by, and therefore equated with, a businessman's or corporation's determination of the economic feasibility of mass production. Congress has not given the slightest hint of an intention to rely here on such judgments. That would, however, be the bottom line result of the Agency's position in many cases. It is wholly unacceptable. It ignores the reality that commercial pharmaceutical manufacturers base their production decisions on economic considerations. If they are commercially manufacturing a product, they have, no doubt, concluded that the pharmaceutical can be safely used. But the converse is not necessarily true. Pharmaceutical companies do not normally manufacture a substance just because it is safe. They manufacture it because they expect to make a profit by so doing.

As when determining "accepted medical use," the only logical source for relevant information on safety is the world of health care practitioners. We turn to the evidence of record in these proceedings.

Findings Of Fact

With respect to the safety of MDMA, the following facts are established in this record by the preponderance of the evidence.

MDMA has been utilized by some psychiatrists as an adjunct to psychotherapy. It is usually administered to the patient only once, or at most twice, at the beginning of a course of psychotherapy. It is administered by, or in the presence of, the treating psychotherapist. The psychiatrist remains with the patient, or is immediately available, during the period after ingesting of the substance when it might adversely affect normal functioning. All of this is in marked contrast to the manner of administering many other controlled drugs,

which patients self-administer at home or elsewhere with scant regard for possible immediate contact with the physician.

There are many other oral medications, controlled substances, that are not so restricted by the treating physician, i.e., to only one or two administrations and in such relatively low doses.

MDMA has been administered to animals in a number of different studies. The injection LD 50[14] has been established and the oral LD 50 has been reliably estimated. The doses of MDMA administered therapeutically by psychiatrists to patients have been less than one percent of the LD 50. This indicates a very high margin of safety with MDMA when it is used in treatment.

Clinical trials with humans were reported in 1978 in a monograph, published by the National Institute on Drug Abuse. Dr. Greer has written a report on his clinical experiences administering MDMA to patients. Others interested in using MDMA in therapy had read copies of this report although it had not been published as of the time of the hearings in this proceeding. Dr. Ingrasci, a psychiatrist in private practice, has reported on his clinical observations in administering the drug to nearly 100 individuals over 5 years, from 1980 to 1985. No evident harm resulted to any of these persons from his use of the drug. Dr. Downing has reported on an informal study of the physiological effects of MDMA on some 20 human volunteers. None of them suffered apparent harm. Although there was no verification by scientific analysis, it is reasonable to accept, in the circumstances, that all these volunteers had ingested MDMA in the quantity assumed for purposes of the study.

In addition, other psychiatrists have been using MDMA in their practices over the past 10 years. Because MDMA cannot be patented, no pharmaceutical

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[14] See finding 27, page 45, below.

company has had the financial incentive to carry out the extensive animal and clinical tests required by the FDA for approval to market the drug on an interstate basis. Nevertheless, the overwhelming weight of medical opinion evidence received in this proceeding concurred that sufficient information on MDMA existed to support a judgment by reputable physicians that MDMA was safe to use under medical supervision. No evidence was produced of any instances where MDMA was used in therapy with less than wholly acceptable safety.

Conclusion

The administrative law judge finds and concludes that there is no "lack of accepted safety for use" of MDMA "under medical supervision." On the contrary, there is accepted safety for use.

VII

Effect Of Secretary's Findings

Issue number 4 is stated:

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

The Agency staff argues that the answer is in the affirmative, pointing to language which it asserts is in § 812 and to one sentence found in House Report No. 91, legislative history of the CSA.

The Agency's brief is in error where it says, on page 32:

> The statutory language of 21 U.S.C. § 812 is clear that
>
> > The recommendation of the Secretary to the Attorney General shall be binding on the Attorney General as to such scientific and medical matters . . . .

(Emphasis added.)

The quoted language is found in § 811, not in § 812.

A careful reading § 811(b) reveals that, before initiating proceedings to schedule a drug, and after gathering data, the Attorney General (i.e., DEA) is to request from the Secretary a scientific and medical evaluation and recommendations as to whether the drug should be controlled. Section 811 then continues:

> In making such evaluation and recommendations, the Secretary shall consider the factors

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> listed in paragraphs (2), (3), (6), (7), and (8) of subsection (c) of this section and any scientific or medical considerations involved in paragraphs (1), (4), and (5) of such subsection . . . . The recommendations of the Secretary to the Attorney General shall be binding on the Attorney General as to such scientific and medical matters . . . .

It is only the scientific and medical factors specified in § 811(c)(2), (3), (6), (7) and (8), and any such considerations as are involved in § 811(c)(1), (4) and (5), on which the Secretary's recommendations are binding. "Currently accepted medical use in practice" and "accepted safety for use" are not mentioned in § 811(c). They appear in § 812, as matters with respect to which "findings" must be made by the Attorney General (DEA) when he is determining which of the five schedules is appropriate. Thus the provision in § 811 for certain recommendations of the Secretary to be binding has no reference at all to "currently accepted medical use" and "accepted safety for use."

The one broad-brush, general statement quoted in the Agency's brief from the Committee Report cannot be read so as to alter the clear language in the statute itself.

The anomalous situation in which the Agency's argument here would put us, i.e., according finality to the recommendation of the Secretary on any questions classifiable as scientific or medical, was pointed up by the Court of Appeals for the District of Columbia Circuit. In its recent opinion in the Buprenorphine scheduling case, the Court observed:

> The intervenor's brief contends, and the Department of Justice agreed at oral argument, that the Administrator's conclusion that buprenorphine is a thebaine derivative can be upheld on an alternative ground. According to these parties, HHS's initial communication to

> DEA stated that buprenorphine is a thebaine derivative, and the Act makes HHS's recommendations as to "scientific and medical matters" binding on the DEA. See 21 U.S.C. § 811(b) (1982). If that were so, it is difficult to see what purpose the agency's on-the-record hearing served in this case. Certainly the Administrator did not appear to regard his independent findings on "scientific and medical matters" as superfluous. While we entertain doubts about the soundness of the Justice Department's interpretation of the Act - Section 811(b) could be read to indicate only that the DEA must follow HHS's recommendations on the specified matters in deciding whether to initiate scheduling actions - our disposition of this case renders it unnecessary for us to decide the point.

Reckitt & Colman, Ltd. v. Administrator, etc. No. 85-1193, April 8, 1986, slip opinion, p. 9, n. (Emphasis added.)

The administrative law judge concludes that the recommendations of the Secretary on the questions of "accepted medical use in practice" and "accepted safety for use . . . under medical supervision," to the extent the Secretary addressed these issues, are not binding on the Administrator of DEA.

VIII

Proper Schedule For MDMA

Introduction

We come to the last of the stated original issues.

> 7. If, on the basis of the resolution of the above issues [including issue 1, the "preliminary issue"], MDMA can lawfully be scheduled in a schedule other than Schedule I, in which schedule should it be placed?

The findings and conclusions of the administrative law judge set out above resolve all the previous issues so as to permit, indeed to require, that MDMA be placed in a schedule other than Schedule I. In which one? We must now focus on the "findings required for each of the Schedules" II through V found in § 812.

Having found that there is a currently accepted medical use for MDMA, and that there is not a lack of accepted safety for use of it under medical supervision, the only matters still to be addressed are the extent of MDMA's potential for abuse, finding (A) for each of these schedules, and the extent of psychological or physical dependence resulting from abuse of it, finding (C) for each of them. The Administrator can place a substance in a schedule only if he "makes . . . the findings prescribed by subsection (b) of section 812 . . . for the schedule in which such drug is to be placed." 21 U.S.C. § 811(a)(1)(B).

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.

2. MDA, or 3,4-methylenedioxyamphetamine, amphetamine and methamphetamine are also phenylisopropylamines.

3. MDA, or 3,4-methylenedioxyamphetamine, is formed by the addition of a methylenedioxy group to amphetamine.

4. MDMA is formed by the addition of a methylenedioxy group to methamphetamine.

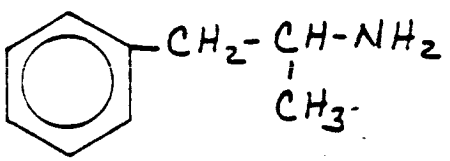
5. The addition of a methylenedioxy group to the aromatic nucleus of amphetamines produces compounds with psychotomimetic activity.

6. Psychotomimetic is a term used to describe a large class of compounds which change or modify a person's mood or mental state. The terms psychotomimetic and hallucinogenic are commonly used interchangebly.

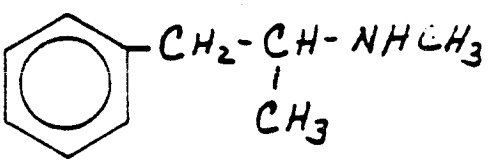
7. MDMA is the N-methyl analog of MDA. This means that MDMA differs structurally from MDA the same way that methamphetamine differs from amphetamine, by the addition of an N-methyl group.

8. N-methylation of amphetamine yields methamphetamine which retains the central nervous system activity of amphetamine.

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



amphetamine



methamphetamine

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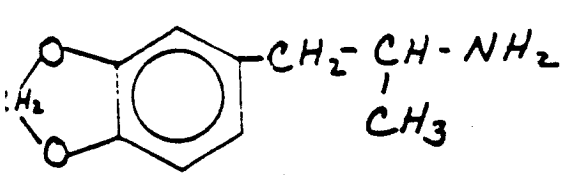
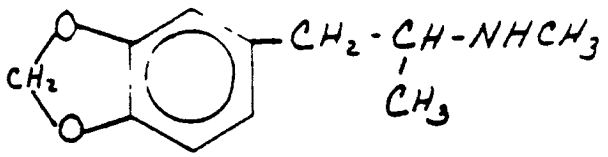
10. The difference in structure between MDA and MDMA is illustrated by the following diagram:



MDA



MDMA

11. This similarity in chemical structure, although of some significance, does not establish that the two substances have identical, or even similar, abuse potential. Nor does the fact that MDMA can be classified as a phenethylamine establish similarity as to abuse potential. Of the 28 phenylethylamines recognized as such by HHS, there are eight which have neither been scheduled in the United States nor recommended for scheduling by the World Health Organization (WHO). Yet the Expert Committee on Drug Abuse of WHO has reviewed the abuse potential of all 28.

12. Research performed by Dr. Harold F. Hardman, an Agency witness, established that mescaline and seven other substances, analogs, have very similar structural formulas, shown below:

No.	MW	5	4	3	R	Name
I	247.4	OCH_3	OCH_3	OCH_3	$CH_2—CH_2—NH_2$	3,4,5-Trimethoxy-β-phenylethyl-amine HCl (mescaline HCl)
II	214.4	H	OCH_3	OCH_3	$CH_2—CH_2—NH_2$	3,4-Dimethoxy-β-phenylethyl-amine HCl
III	200.0	H	O—CH_2—O		$CH_2—CH_2—NH_2$	3,4-Methylenedioxy-β-phenyl-ethylamine HCl
IV	215.5	H	O—CH_2—O		$CH_2—\underset{\displaystyle CH_3}{\underset{\vert}{CH}}—NH_2$	3,4-Methylenedioxy-α-methyl-β-phenylethylamine HCl
V	229.0	H	O—CH_2—O		$CH_2—\underset{\displaystyle CH_2\\ \displaystyle CH_3}{\underset{\vert\\ \vert}{CH}}—NH_2$	3,4-Methylenedioxy-α-ethyl-β-phenylethylamine HCl
VI	231.0	H	OCH_3	OCH_3	$CH_2—\underset{\displaystyle CH_3}{\underset{\vert}{CH}}—NH_2$	3,4-Dimethoxy-α-methyl-β-phenylethylamine HCl
VII	261.4	OCH_3	OCH_3	OCH_3	$CH_2—\underset{\displaystyle CH_3}{\underset{\vert}{CH}}—NH_2$	3,4,5-Trimethoxy-α-methyl-β-phenylethylamine HCl
VIII	229.4	H	O—CH_2—O		$CH_2—\underset{\displaystyle CH_3}{\underset{\vert}{CH}}—NH—CH_3$	3,4-Methylenedioxy-N,α-dimethyl-β-phenylethyl-amine

In the above listing, substance I is mescaline, substance IV is MDA and VIII is MDMA. From columns "4" and "3" we see that substances III, IV (MDA), V and VIII (MDMA) all have the methylenedioxy group added to amphetamine. Yet substances III and V are not scheduled drugs. DEA has not found them to have significant abuse potential, despite their close structural similarity to MDA and MDMA.

13. Chemical similarity may or may not be a good guide to the actual effects of a compound in the human body.

14. MDMA produces pharmacological effects in common with both central nervous system stimulants like amphetamine, and hallucinogens like MDA, in animals.

15. MDA and MDMA both produce central nervous system stimulation in animals as measured by increased locomotor activity in mice.

16. 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 on man."

17. A study conducted by Intox Laboratories reported significantly reduced body weights at 7 and 14 days following initiation of MDMA dosing in rats.

18. The Intox Laboratory study also reported that rats who had been administered MDMA showed hyperactivity, excitability, aggressive behavior and stereotypic behavior.

19. 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.

20. 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.

21. MDA and MDMA both produce an increase in body temperature when administered to rabbits at similar potencies. Hyperthermia in rabbits is reported to be a measure of central nervous system activity. 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.

22. The preceeding eight findings demonstrate that it is appropriate to classify MDMA as a central nervous system (CNS) stimulant. Although MDMA may be so classified, there are many other substances which are CNS stimulants but which are not currently controlled in the United States nor have been recommended for control by WHO. Caffeine is one such substance. Others, whose abuse potential has been reviewed by WHO, are clobenzorex, fenbutrazate, furfenorex, morazone, para-oxyamphetamine, and N, N-dimethylamphetamine.

23. Categorizing a substance as a CNS stimulant is of little assistance in determining whether or not it has a potential for abuse or what relative degree of abuse potential it may have.

24. 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.

25. Two substances classified by HHS as hallucinogens have not been scheduled in the United States nor have they been recommended by WHO, after

review, for scheduling. They are 4-bromo-2, 5-dimethoxyphenethylamine and N-ethyl-3, 4-methylenedioxyamphetamine. Thus, categorizing a substance as a hallucinogen is of little assistance in determining whether or not that substance has a potential for abuse or what relative degree of abuse potential it may have.

26. In mice, dogs and monkeys, MDA and MDMA produce the same spectrum of pharmacological effects when observed during toxicity studies. 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. These effects are part of what is described as the classical pharmacological response of the dog to intravenous mescaline.

27. The lethality of a compound is reported as an LD50, which is the dose of a drug which will kill 50% of the animals receiving that dose.

28. The LD50's for mescaline, MDA and MDMA were determined by intravenous[15] or intraperitoneal[16] 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.

29. Intraperitoneal LD50's for MDA and MDMA were determined in mice by Davis. 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. 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.

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15 into a vein.
16 into the abdominal cavity.

30. In the study conducted by Intox Laboratories the oral LD50 for MDMA in rats was estimated to be approximately 325 mg./kg. 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.

31. Every drug has an LD50. The preceeding four findings as to LD50 have nothing to do with establishing the abuse potential of MDMA. A value that is of interest, however, is the therapeutic index, i.e., the ratio of the LD50 to the effective dose (ED50). How close is the dose which will kill 50% of the tested animals to the dose required for the desired effect in humans? If these two doses are very close to each other, then there is an obvious danger in using the drug with humans.

32. Most general anesthetics have a very low therapeutic index of two to one, i.e., just twice the quantity commonly used in medical practice is sufficient to kill. Yet these anesthetics are used by doctors all the time, under carefully controlled conditions.

33. The estimated oral LD50 for MDMA in rats, as noted above, is 325 mg./kg., i.e., 325 mg. of MDMA per kilogram of weight of the rat. The effective oral human dose is 2 mg./kg. of weight. Thus there appears to be a comparatively large margin of safety in the use of MDMA in humans - the LD50 is 160 times the ED50 in humans.

34. MDMA, MDA, amphetamine and methamphetamine produce effects that are neurotoxic, i.e., nerve destructive, when administered to animals. MDMA and MDA are neurotoxic in rats at doses which are very low compared to the neurotoxic doses of amphetamine and methamphetamine.

35. MDMA and MDA both produce long term reduction in serotonin levels and uptake sites in the rat brain. These neurochemical depletions are due to

the destruction of serotonin nerve terminals as determined by visual staining techniques.

36. 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.

37. Although single injections of MDMA may be slightly less neurotoxic than MDA, chronic use of MDMA appears to be more neurotoxic than MDA. The relevance and materiality of this conclusion to the report of the study on which this conclusion was based indicates only that the MDMA was injected into rats. The route of injection, which will make a vast difference in the meaning of the results noted, is not given in the report. Humans are known to take MDMA orally, not by injection. This difference is of great importance, and renders the test results meaningless for our purpose.

38. The neurotoxicity of amphetamine and methamphetamine has been determined in rats, guinea pigs and monkeys.

39. MDMA and MDA are suspected of having the potential to produce the same neurotoxic effects to serotonergic nerves in humans, but there is very little evidence to support this suspicion.

40. On the other hand, the drug fenfluramine has been determined to produce the biochemical effects in rats of which MDMA is suspected, but at much lower dosage levels than in the case of MDMA. In fact, the proven dosage levels of fenfluramine causing these effects are merely 1.25 times its ED50 when used for anorexia in humans. Nontheless, FDA has approved the daily use of fenfluramine in humans on a chronic basis. Fenfluramine is a controlled substance, but this proven neurotoxic substance is only in Schedule IV.

41. Drug discrimination studies in animals allow one to determine if a particular dose of a test substance produces in the animal effects which are recognized by the animal as the same as those produced by a particular dose of another substance. 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.

42. 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.

43. MDMA shares discriminative stimulus properties in common with amphetamine and MDA in drug discrimination studies in rats.

44. 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.

45. Rats trained to recognize MDA recognized MDMA, in drug discrimination studies conducted by Dr. Glennon, as hving some properties similar to MDA.

46. 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.

47. MDA is unique among chemicals in being recognized by animals who are trained to recognize hallucinogens and also by animals trained to recognize stimulants. MDMA does not share this dual response characteristic of MDA. The overwhelming weight of the evidence in this record is that MDMA is not properly classified as a hallucinogen. One witness disagrees. His disagreement results from reports he has received from street users, who are widely regarded as an unreliable source of information as to specifics on any matter. There are no results of controlled scientific experiments in the record establishing MDMA to be a hallucinogen in humans. Animals trained to recognize MDA who also respond to MDMA are, more likely than not, responding to the CNS stimulant characteristic of MDMA rather than to any hallucinogenic properties.

48. The significance of animal discrimination test findings as to abuse potential in humans is far from certain. An Agency witness in this proceeding co-authored an article, published in 1984, which states that unless a particular compound has been tested in humans, one cannot be certain that structure-activity relationships will apply in the clinical situation, i.e., when used in humans. He cautioned that the most common error found in animal models is the identification of "false positives". That is, the animal models may indicate a compound to be active, whereas actual testing in humans reveals inactivity. The article also says that it is clear that no present animal models correlate with the qualitative differences between hallucinogens observed in humans.

49. In 1984 the National Institute of Drug Abuse (NIDA) reviewed DEA's initial proposal for the placing of MDMA in Schedule I. NIDA reported to

Dr. Edward Tocus of the FDA that: "The direct evidence that MDMA has any abuse potential in animals is not substantiated, based on the data DEA provided." GG 55.[17]

50. 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.

51. As our hearings were concluding it was learned that tests were being conducted with rhesus monkeys and baboons trained to self-administer cocaine to see if the monkeys and baboons would continue to self-administer when MDMA was substituted for the cocaine. Preliminary reports were obtained from those conducting these tests. These reports were placed in evidence by the Agency. Upon study of them, and of the Response to them dated November 4, 1985 by Drs. Grinspoon, et al., the administrative law judge finds that these preliminary reports lack sufficient indicia of reliability to be given any weight. They certainly fail to buttress the Agency's position that MDMA has "a high potential for abuse" in humans. They are immaterial.

52. Drs. Shulgin and Nichols first reported that MDMA produces psychotomimetic effects in man in 1976. These effects are described as intoxication, an easily controlled altered state of consciousness and sympathomimetic stimulation.

17/ "GG" = Drs. Grinspoon, et al., exhibit; "G" = Agency exhibit.

53. 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.

54. 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 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.

55. 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. A slight 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 slight increase in motor activity lasted several more hours. Shulgin concluded that the "psychopharmacological profiles" of MDA and MDMA and two other compounds are very similar. However, five years later Shulgin wrote: "There can be little validity in an argument that the psychopharmacology of MDMA can be predicted from that of MDA. The facts are otherwise." GG 30, p.3.

56. There are observed differences in humans between the effects of MDA and MDMA. Studies other than the one reported by Shulgin in 1980 have shown MDA to have duration of action in humans of 12 to 15 hours, as compared to four to six hours for MDMA. MDA has been found to produce a mild cognitive impairment in humans at the 75mg. dosage level, while MDMA did not impair cognition

even at 200mg. As MDA dosages increase from 75 to 200mg., the effects in humans become increasingly similar to the effects of LSD, including the presence of visions. As dosages of MDMA increase from 75 to 200mg., the intensity of the sense of wellbeing and inner flow of associations which characterize the experience increase only moderately while the ego functions remain intact, cognition is unimpaired and visions are notably absent. Large doses of MDA (200mg) produce significantly greater disorientation and an up-welling of visual images that are not characteristic of MDMA in similar dose range.

57. The dosage comparisons just referred to are those using the levo-rotary optical isomer of MDA. There are clear indications that this isomer of MDA is more active than either the racemic mixture or the dextro-rotary isomer. It was the racemic mixture of MDMA that was used in the studies referred to immediately above.

58. The uncontradicted evidence of record is that there are qualitative differences in humans between MDA and MDMA.

59. The Agency presented testimony from a staff member of only one of the many drug abuse clinics in the country, the Haight-Ashbury Free Medical Clinic in San Francisco. This clinic treats approximately three to four clients per month who seek help for problems arising from the use of one or more of a group of five or six different drugs which the clinic lumps together in its statistics. MDMA is one of these drugs. The clinic has no reliable figures on how many of these three to four patients per month have been reporting abuse of MDMA specifically. Even if the three or four clients mentioned all reported using MDMA, that would constitute less than one percent of the clinic's total of about 450 clients per month. The clinic has no way of knowing whether any of

its relatively small number of clients reporting MDMA use were actually using MDMA -no reliable testing has been done. Many of the drugs sold on the street to persons such as the clients of this clinic are not, in fact, what they are represented to be by the seller. The numbers, three to four clients per month reporting use of MDMA or any one of the other drugs lumped together with it statistically by this clinic, has remained fairly constant for the last 15 years. In that 15 year period there has been only one instance of a client reporting use of MDMA and producing a pill of the type he said he had been taking which was analyzed and was reliably reported to be MDMA. Two other pills, brought in by other clients reporting them to be samples of MDMA, turned out to be not MDMA but, rather, MDA.

60. During the year preceeding April 24, 1985 there were no reported incidents of abuse of MDMA, or of complications resulting from its use, in the Philadelphia, PA, area. No such instances in New York City or in Boston during that period were brought to the attention of a staff psychiatrist at a Veterans Administration Hospital drug abuse clinic in Philadelphia who has talked with colleagues in those cities.

61. In the Los Angeles area there was a noticeable increase in the street use of MDMA shortly before its becoming illegal on July 1, 1985. This coincided with the attention MDMA received in the news media at that time. There was also a significant increase in the manufacture of MDMA at that time, much of which was to permit stockpiling of supplies before the July 1, 1985 ban went into effect. This manufacturing was done by those who supplied the street market. It has been estimated that in all of 1976, 10,000 doses of MDMA were distributed in the United States for street use, as opposed to 30,000 doses per month in 1985. These estimates are based on information obtained from street users. Street users are notoriously unreliable in matters of specific information. No reliable conclusion as to number of users can be gleaned from these

estimated figures. In 1985 the most common patterns of non-medical use of MDMA found in Los Angeles were "experimental" (ten times or less in lifetime history) or "social-recreational" (one to four times per month).

62. Cocaine poses many more, and much more serious, social problems for this country than did MDMA before it was banned. Street drug users in Los Angeles did not find it as appealing as cocaine. Cocaine is very rewarding and produces pleasurable sensations in the brain that causes the brain to try to repeat the experience. Cocaine has the potential for producing a lot of repetitive drug taking. It produces tolerance and, in an effort to overcome the tolerance, people repeat the experience again and again. Substances considered to be similar to MDMA in their effects on humans have not been used in that way, according to studies of drug users made over the last 20 to 30 years.

63. The circumstances and surroundings in which MDMA is taken, or in which one who has recently ingested MDMA finds himself, has an effect on the reactions and perceptions of the subject while the drug is still effective within his system.

64. Low to moderate doses of MDMA have been given to individuals by wholly legitimate and highly regarded psychiatrists as an adjunct to psychotherapy. Some of the MDMA so administered was made by them under the supervision of Dr. Shulgin in his laboratory in California.

65. MDMA has been reported, by the psychiatrists administering it to themselves and others, and by other individuals, to produce at one time or another some or all of 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, vomiting, headache and shakiness.

66. Psychological effects reported for low to moderate doses of MDMA, in various subjects at various times, include gentle euphoria, sense of well-being and peacefulness, 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.

67. MDMA was first identified by a DEA laboratory in 1972. Between 1972 and April 1985, DEA laboratories had identified 41 exhibits of MDMA consisting of over 60,000 dosage units.

68. 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.

69. 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.

70. Since 1978, nonfederal forensic laboratories have reported at least 41 exhibits of MDMA to DEA.

71. Pharm Chem Laboratories and Toxicology Testing Service are laboratories which provide confidential analysis of drug samples voluntarily submitted to them. Their data provides some useful information on the availability of street drugs and trends in drug abuse patterns.

72. 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. This evidence is of little help to us since we are not told how many of the 610 total submissions

were MDA and how many were MDMA. It is worth noting that the highest number of combined MDA/MDMA submissions to Pharm Chem was 88 in 1978. Only 22 such submissions were reported in 1983.

73. Pharm Chem reported 20 submissions of MDMA between May 1983 and May 1984 when it discontinued its testing service.

74. Toxicology Testing Service reported 15 submissions of MDMA between April 1, 1984 and March 31, 1985.

75. In its investigation of the clandestine manufacture of controlled substances, DEA has seized four clandestine laboratories producing, or possessing the necessary chemicals to produce, MDMA during the 13 year period 1972 through 1984. A total of about 2,400 clandestine laboratories were seized during that period. During the seven year period 1977 through 1983, 31 clandestine laboratories having the capacity to produce MDA were seized. Impurities found in the MDMA analyzed by forensic laboratories indicate that MDMA is produced in clandestine laboratories.

76. A DEA investigation conducted in June 1984, of a suspected cocaine distributor produced information that a drug known as "Ecstasy" was being sold in the Dallas, Texas area. Samples were obtained through undercover buys in that area in February and March 1985. Analysis revealed each tablet to contain 110mg. of MDMA. In April 1985 "Ecstasy" was widely available on the street in the Dallas area. It was reported to DEA agents in March 1985 that "Ecstasy" was being shipped to the Dallas area in cases containing 100 tablet bottles from California. It was at that time being marketed in the Dallas area in a manner similar to that in which structured illicit drug trafficking

organizations operate. At that time it was not illegal to manufacture, sell or possess MDMA under the Federal CSA. The record is unclear as to whether or not these actions were illegal under Texas State law at that time.

77. Street prices for MDMA in 1984 were listed as $70 per gram in New York and $20 per capsule in New Hampshire in an underground flier.

78. Students at the University of Texas in Austin indicate that MDMA is easily available on campus at about $5 to $20 a tablet.

79. Dr. Richard P. Ingrasci has interviewed over 500 individuals who have used MDMA over the past seven to eight years. A little more than half of these individuals had used MDMA in a non-therapeutically motivated setting, out of curiosity or for recreation.

80. Dr. Joseph J. Downing, a practicing psychiatrist in San Francisco, CA, conducted a pilot study in 1984 into the effects in healthy humans of a single exposure to MDMA. The 21 subjects in Dr. Downing's MDMA study had all used MDMA previously. One had used MDMA 15 times, one 10 times, and one only once. The mean frequency of use of the 21 subjects was once every 2.2 months.

81. Dr. Lester Grinspoon reports that MDMA is being taken by a growing number of people, particularly students and young professionals. The text cited by Government counsel does not indicate to what extent this use is in a therapeutic setting or is in a casual or recreational manner.

82. Dr. George Greer, a practicing psychiatrist in Santa Fe, New Mexico, has used MDMA as an adjunct to psychotherapy in clinical work. He reported that one of his subjects, after taking the unusually high dosage of 350mg. of MDMA, reported a brief hallucination, a brief visual illusion, a mild

hearing impairment, a brief memory loss and a brief distortion in depth preception.

83. The National Institute on Drug Abuse (NIDA) publishes annually a compilation of drug abuse information collected through its Drug Abuse Warning Network (DAWN). This data collection system collects reports from selected (currently more than 700) hospital emergency rooms in the United States. The reports collected record all visits to those emergency rooms for medical problems associated with drug abuse. According to NIDA, the major objectives of the DAWN system include the following:

> To monitor drug abuse patterns and trends and to detect new abuse entities and new combinations;
>
> To assess health hazards associated with drug abuse.

84. The record reflects that from 1972 through September 15, 1983, there were only eight mentions of MDMA in the DAWN system. During the period 1972 through 1983, the DAWN system was reporting approximately 175,000 drug mentions each year. Thus, the eight mentions of MDMA occurred during a period during which DAWN reported roughly 2 million mentions of other drugs. The few mentions here of MDMA are far less than those of such Schedule I drugs as heroin, marijuana, and LSD. During the time period that MDMA was mentioned 8 times, MDA, a Schedule I drug, was mentioned 344 times — more than 40 times as frequently. MDMA does not compare with the frequency with which Schedule II drugs appear in the DAWN reports, nor even with the mentions of Schedule III drugs or Schedule IV drugs found there. The FDA of the Department of HHS called the eight DAWN mentions of MDMA "not significant except to indicate the existence of human use of MDMA."

85. MDMA is reported to have been associated with two overdose deaths. One death occurred in Seattle, Washington in 1979. However, the evidence in the

record does not permit a finding that MDMA was, in fact, involved in that death. A careful reading of the toxicology report shows that the involvement of MDMA there is questionable. The second reported association, in Santa Monica, California, is even more questionable. There is no toxicology report at all in this record with regard to it. The evidence does not permit a finding that MDMA was, in fact, associated with that death, either.

86. The record of the FDA-HHS consideration of MDMA is as follows.

87. The relevant staff member at FDA, Dr. Edward Tocus, reviewed the DEA Control Recommendation proposing that MDMA be placed in Schedule I (G B-2). He subsequently prepared a one-and-one-half page document which included both a summary and an evaluation of the Recommendation.

88. Dr. Greer, practicing psychiatrist in New Mexico, had previously written to the Assistant Secretary for Health about Dr. Greer's therapeutic work with MDMA. Dr. Greer had also written to an FDA staff member (Mr. Contrera), a supervising pharmacologist who worked for Dr. Tocus, about Dr. Greer's work with MDMA, enclosing a copy of his report of his work with MDMA (GG 14). Dr. Tocus was not aware of these prior contacts between Dr. Greer and the FDA when Dr. Tocus wrote his MDMA control evaluation and prepared related papers for his superiors at HHS.

89. At the time Dr. Tocus reviewed the DEA recommendation and prepared the HHS documents for his superiors, he believed that the statutory phrase "accepted medical use in treatment in the United States" meant that a drug had to have been approved by the FDA for interstate shipment and sale pursuant to the FDCA. Further, Dr. Tocus believed that, based on his understanding of the law, if HHS came to the conclusion that a drug should be scheduled but it had not been approved for interstate shipment and sale,..pursuant to the FDCA, "that

the only alternatives were Schedule I [if it had any abuse potential] or no schedule at all." (Tr 9, at 67)

90. Before formulating its recommendations on MDMA, the FDA and HHS did not consult any organization of medical professionals. Dr. Tocus testified that he did not take any action to make inquiries about medical opinion on MDMA even though he had been told on a hearsay basis that there was some therapeutic interest in the drug. The Department of HHS did not refer the issue of the appropriate scheduling of MDMA to the FDA's Drug Abuse Advisory Committee. This Committee is made up of authorities knowledgeable in the medical, behavioral and biological sciences as they apply to drug abuse. Its Charter, signed by the Secretary of HHS, states:

> The Committee advises the Commissioner of Food and Drugs regarding the scientific and medical evaluation of all information gathered by the Department of Health and Human Services and the Department of Justice with regard to safety, efficacy, and abuse potential of drugs or other substances and recommends actions to be taken by the Department of Health and Human Services with regard to marketing, investigations, and control of such drugs or other substances.

GG 62 (Emphasis added). No one at FDA had the benefit of any input from this Committee with respect to MDMA.

91. Dr. Tocus made six typographical corrections to the original DEA recommendation for Schedule I placement of MDMA. These corrections are set out in GG 59. Dr. Tocus then prepared his one-and-one-half page summary and analysis or evaluation of the DEA scheduling recommendation. (G B-4)

92. The recommendation Dr. Tocus prepared for his superiors does not mention that Dr. Tocus had been informed orally that there was therapeutic interest in MDMA, or that Dr. Greer had previously communicated his interest in

MDMA, and actual use of it in therapy, to the Assistant Secretary for Health and to the FDA.

93. The recommendation prepared by Dr. Tocus for his superiors never discusses or comments on "accepted medical use in treatment" or "accepted safety for use under medical supervision." It includes a single sentence asserting that: "There is no known legitimate use of MDMA in humans." (G B-4 at 2) This key statement was inaccurate.

94. Dr. Tocus testified that he forwarded his one-and-one-half page evaluation (G B-4) and the DEA's evaluation (GG 56) to the Acting Commissioner of FDA and thence to the Assistant Secretary for Health.

95. Before forwarding the papers Dr. Tocus requested comments on the DEA proposal to schedule MDMA in Schedule I from the National Institute on Drug Abuse (NIDA) — as he was required to do by HHS departmental procedures. The National Institute on Drug Abuse responded in memorandum form. GG 55. The NIDA memorandum states that: "The direct evidence that MDMA has any abuse potential in animals is not substantiated, based on the data DEA provided." That memorandum, noting that there have been some reports of MDMA use outside the medical context, concludes that "NIDA does not have any objection to placing MDMA under Schedule I of the CSA." But NIDA reaches no conclusion that MDMA has a "high" potential for abuse. The NIDA memorandum gives no indication of an opinion as to <u>any</u> level of potential for abuse in MDMA.

96. The NIDA memorandum was <u>not</u> forwarded to the Commissioner of the FDA and was <u>not</u> forwarded to the Assistant Secretary for Health. Dr. Tocus was aware of the views of NIDA prior to receiving the NIDA memorandum. He shared the NIDA view that the evidence did not substantiate abuse potential in animals. But those judgments were not reflected in the materials that Dr. Tocus

forwarded to the Acting Commissioner of Food and Drugs or to the Assistant Secretary for Health.

97. None of the underlying documents prepared at the Department of HHS ever reached the conclusion that MDMA had a "high" potential for abuse. The one-and-one-half page memorandum prepared by Dr. Tocus notes on page one that DEA has concluded that MDMA has a high potential for abuse. But the HHS evaluation itself never so concludes.

98. Based on this record, the Acting Commissioner of Food and Drugs forwarded the package on to the Assistant Secretary of Health. The Acting Commissioner stated his conclusion to be only that "MDMA has a significant potential for abuse." (GG 54) He made no mention of "a high potential for abuse," which is what the CSA requires for Schedule I or Schedule II placement.

99. The formal response to DEA from HHS, signed by the Assistant Secretary for Health, does state that: "We believe MDMA has a high potential for abuse" and recommends Schedule I placement. (G B-3) This difference as to degree of abuse potential between "significant" and "high" represents a quantum increase from the memorandum of the Acting Commissioner to the letter of the Assistant Secretary for which there is no basis in the record of HHS' consideration.

100. DEA was unaware of the therapeutic use to which MDMA had been put by Dr. Greer and other doctors when it prepared its initial recommendation for placing MDMA in Schedule I (G B-2) and sent it to HHS.

Discussion

The Agency staff has the burden here of establishing that MDMA has a "high" potential for abuse. It has not carried that burden. A "high" potential is required by the CSA for placement in either Schedule I or Schedule II.

The evidence as to the meaning of similarity of chemical structure between MDMA and other substances is inconclusive. There is similarity, for example, between MDMA and MDA, which is a CSA Schedule I substance. But there is comparable similarity between these two drugs and two others which have not been found to have any abuse potential and which are not scheduled at all. See finding 12, page 42. MDMA is classified as a phenethylamine. Some phenethylamines are scheduled under the CSA, but others are not. WHO has reviewed the abuse potential of 28 phenethylamines. It has recommended only some of those 28 for scheduling. Of those 28, there are eight which have neither been scheduled at all in the United States nor recommended for scheduling by WHO. See finding 11, page 41.

The great preponderance of the evidence in this record is to the effect that MDMA is not properly classified as a hallucinogen. There is some expression of opinion to the contrary. Even if it is classified as such, that fact would not establish a "high" potential for abuse in humans. There are at least two known hallucinogens which have not been scheduled at all in the United States. See finding 25, pages 44 and 45.

Animal tests have shown MDMA to be a central nervous system stimulant. MDA, a Schedule I substance, is a central nervous stimulant. But that fact does not establish that MDMA should also be placed in Schedule I. Many other substances

also act as central nervous stimulants which are not scheduled at all. See finding 22, page 44.

The other animal test results in the record are equally inconclusive as to abuse potential. See findings 37, 40, and 47, above.

There are reports of non-medical use of MDMA by humans. These reports do establish that MDMA has a potential for abuse. But before it can be said that, in the context of § 812, MDMA has a "high" potential for abuse, the known facts as to MDMA must be compared with the known facts as to human abuse of other substances. When these comparisons are made, it cannot be concluded that the facts show MDMA to have a "high" potential for abuse. See findings 59, 62, 72, and 84, above.

Upon close examination the material received from HHS is of little assistance to us in this case. No independent tests, studies or scientific examinations were made there. Relevant and material facts and opinions, within the knowledge of some at FDA, were not brought to the attention of higher officials, including the Assistant Secretary who signed the formal communication to the Administrator of DEA.

The staff person at FDA responsible in this matter had a misunderstanding of the law's requirements from the outset. He was of the misapprehension that a substance with <u>any</u> degree of potential for abuse <u>had</u> to be placed in Schedule I if it lacked an IND, or NDA, granted by FDA.

FDA did not see fit to consult its panel of experts created for the purpose, the Drug Abuse Advisory Committee. That group would undoubtedly have had helpful input for our consideration of the "acceptable medical use" issue, and the "degree of abuse potential" issue, among others.

There are no "binding" recommendations in the HHS letter of June 6, 1984 (G B-3) and its enclosure (G B-4) such as are contemplated by 21 U.S.C. § 811(b). The only recommendation stated is as to the schedule into which MDMA should be put. This is, of course, the ultimate question to be determined and the Secretary's recommendation on it, though entitled to consideration, is not made "binding" by the statute. For the rest, the response from HHS contains some factual recitals, largely repeating or summarizing the data initially sent to it by DEA, and some expressions of opinion - interesting in that they do not give much support to the one recommendation made. For instance, FDA observes on page 2 of G B-4 that the rate of MDMA mentions in the DAWN reports "is not significant except to indicate the existence of human use of MDMA." It is also there observed that the difference in numbers of DAWN mentions between MDMA and MDA "is considered to be more an indication of availability rather than degree of toxicity." The observation that "there is no known legitimate use of MDMA in humans" is incorrect as a factual statement. If it is intended to reflect an interpretation of the statute, it is entitled to consideration, which it has received, supra, but it is certainly not binding.

These critical observations are, regrettably, essential if we are to put the formal recommendation of the Assistant Secretary into proper focus and determine the weight of which it is deserving. In the circumstances, it appears to be deserving of very little weight.

Conclusion

The evidence of record does not establish that, in the context of § 812, MDMA has a "high potential for abuse." Accordingly, it cannot be placed in

Schedule II. (We have already seen that it cannot be placed in Schedule I, because it does have "a currently accepted medical use in treatment" and it does not "lack . . . accepted safety for use . . . under medical supervision.")

No one has argued here that the evidence establishes that MDMA "may lead to severe psychological or physical dependence," another requirement for Schedule II placement. The evidence does not so establish. For this reason, also, MDMA cannot be placed in Schedule II.

Mr. Ehrnstein argues that MDMA cannot be scheduled at all because HHS has not performed such a scientific and medical evaluation as the CSA calls for. He asserts that this failure deprives DEA of "jurisdiction" to schedule the drug. The administrative law judge rejects this argument. The statute requires DEA to "request" an evaluation from HHS. DEA did so. HHS did send a recommendation to DEA. DEA is considering that recommendation. The minimum statutory requirements have been met in this case.

Mr. Ehrnstein also argues that the evidence establishes no abuse potential sufficient to place MDMA in any of the five schedules. The administrative law judge agrees, and accepts this argument, as to Schedule II. The judge disagrees with, and rejects, the remainder of the argument. There is ample evidence of <u>some</u> abuse potential in the record.

Drs. Grinspoon, <u>et al.</u>, argue that sufficient evidence of abuse potential has been shown to warrant placing of MDMA in Schedule III. The administrative law judge agrees, concluding that the evidence does establish MDMA to have "potential for abuse less than the drugs or other substances in Schedules I and II," and to establish that abuse of MDMA "may lead to moderate or low physical dependence or high psychological dependence." 21 U.S.C. § 812(b)(3).

The administrative law judge concludes that the evidence of record requires MDMA to be placed in Schedule III.

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IX

Recommended Decision

Drs. Grinspoon, et al., assert that there are two courses of action open to the Administrator at this point: Either the Administrator can review all the evidence of record and reach a decision, based thereon, on all the issues, or the Administrator can send the record, together with the administrative law judge's findings and conclusions, to HHS for review and comment on the scientific and medical issues.

The administrative law judge finds neither authority nor merit for the second alternative.

The statute clearly provides that, in a situation such as ours, where DEA initiates a scheduling, DEA shall, "before initiating proceedings" and after gathering necessary data, request an evaluation and recommendations from HHS. 21 U.S.C. § 811(b). That was done. After HHS responded to the request, DEA initiated this proceeding. The statutory scheme clearly contemplates that at that point opportunity will be provided, in open hearings pursuant to the Administrative Procedure Act, for the presentation of further "data" or evidence on all issues. The Administrator is then to make the final Agency decision, which must be based on that record. The statute contemplates that the record may contain scientific and medical information not considered by HHS at the outset.

Referral of the matter at this point to HHS for a second time may well result in a record that could not pass muster under the Administrative Procedure Act.

The Administrator of DEA has no authority to direct the Secretary of HHS to take any action. The Administrator provided the Secretary with the opportunity the statute requires.

If the Administrator of DEA carefully considers the entire record now provided in this proceeding, there is no reason why he cannot come to the informed decision the law requires of him as the Agency head.

Needless to say, nothing in this opinion is to be taken as being in any way critical of the Agency's emergency scheduling of MDMA which became effective on July 1, 1985. That action was taken pursuant to certain statutory authority with which this proceeding is not concerned. That action was wholly unilateral, reflecting a view based on evidence then available to the Agency but without opportunity for the presentation of countervailing evidence or argument. This proceeding, a wholly separate process, has provided that opportunity. A complete record, with input from different perspectives, has now been assembled for the benefit of the Administrator, the head of the Agency.

The record now assembled contains much more material about MDMA than the Agency was aware of when it initiated this proceeding by publishing a notice almost two years ago.

Based upon this record it is the recommended decision of the administrative law judge that the substance 3, 4-methylenedioxymethamphetamine, also known as MDMA, should be placed in Schedule III.

Dated: MAY 22 1986

Francis L. Young
Administrative Law Judge

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PUBLIC LAW 98-329 [H.R. 4201]; June 29, 1984

CONTROLLED SUBSTANCES ACT; RESCHEDULING OF METHAQUALONE

For Legislative History of Act, see p. 540

An Act to provide for the rescheduling of methaqualone into schedule I of the Controlled Substances Act, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That, notwithstanding the schedule requirements of section 202(a) of the Controlled Substances Act (21 U.S.C. 812(a)) and the requirements of section 201 of such Act (21 U.S.C. 811) respecting the scheduling of controlled substances, the Attorney General shall, by order, transfer methaqualone from schedule II of such Act to schedule I of such Act. The transfer shall take effect not later than the expiration of ninety days from the date of the enactment of this Act.

SEC. 2. Effective thirty days after the date methaqualone is transferred to schedule I of the Controlled Substances Act, the Secretary of Health and Human Services shall by order withdraw the approval under section 505 of the Federal Food, Drug, and Cosmetic Act of the new drug application for methaqualone.

Approved June 29, 1984.

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CERTIFICATION OF SERVICE

This is to certify that the undersigned on MAY 22 1986 caused a copy of the foregoing to be delivered to:

Stephen E. Stone, Esq.
Charlotte A. Johnson, Esq.
Office of Chief Counsel
Drug Enforcement Administration
1405 I Street, N.W.
Washington, D.C. 20537
Counsel for the Government

and caused a copy to be mailed, postage paid, to each of the following:

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Counsel for Thomas B. Roberts, Ph.D.,
George Greer, M.D., James Bakalar and
Lester Grinspoon, M.D.

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Melanie L. Baltz
Hearing Clerk

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THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

The University of North Carolina at Chapel Hill
School of Medicine
Biological Sciences Research Center 220 H
Chapel Hill, N.C. 27514

April 24, 1985

Mr. Richard Cotten
Dewey, Ballentine, Bushby, Palmer and Wood
1775 Pennsylvania Avenue N.W.
Washington, D.C. 20006

Dear Mr. Cotten:

I have gone over almost all of the material you sent me. This includes reprints of published material, preprints of material to be published, some correspondence, and finally, the position paper presented by the Drug Enforcement Agency and supported by Dr. Edward Brandt, the former Assistant Secretary for Health in the Department of Health and Human Services. These two statements attempt to justify scheduling methylenedioxymethamphetamine (MDMA) in Schedule I of the Controlled Substance Act (CSA). My conclusion, after reading all of this material is that MDMA is an extraordinarily interesting compound which deserves further investigation at both the basic science and clinical level. Scheduling it as Class I is probably an error and is certainly premature. It will inhibit research by making the federal review process more cumbersome for those who seek INDs for such work and it adds on the additional bureaucratic burden of special approval that several states require for Schedule I drugs. I would advocate that MDMA be a Schedule III drug, open to investigation by interested, responsible investigators in appropriate settings.

The DEA offers six arguments for using Schedule I. All of them have partial and superficial truth, but all of them are subject to different honest interpretation. Let me consider these one by one.

1. MDMA is an analog of 3,4 methylenedioxyamphetamine (MDA), a Schedule I substance. This statement is true, but chemical "analog" does not mean identity nor even necessarily great similarity in terms of biological action. We know many compounds where analogous chemical structures have quite different effects. Among the steroids, male and female sex hormones are analogous, but obviously yield different sexual differentiation. The glucocorticoids are analogous to the electrocorticoids, but the one controls glucose metabolism; the other electrolytes. Ritalin and

dextroamphetamine are analogous amphetamines and are approximately equally effective when used in the treatment of hyperactivity and attention deficit disorders in children. But, recent work shows that they effect catecholamine metabolism in directly opposite ways. In those cases in which chemical analogs have identical action, there is usually conversion of the one to the other in the body. Thus, imipramine and desmethylimipramine are chemically analogous and also pharmacologically analogous. It is because in the body one is converted to the other. In the case of MDMA compared to MDA, there is no evidence of conversion at this time. Indeed, this is an area of research which should be vigorously pursued. If the compounds are converted into each other in the body, the case for pharmacological similarity or even identity would be greatly strengthened. If they are not so converted, the compounds should be considered to be quite different regardless of their chemical similarity. There is some indirect evidence that the two compounds are biologically quite dissimilar. Clinically, MDMA has a shorter duration of action than MDA. Tolerance is reported to occur with the repeated use of either compound but there is no reported cross tolerance between them. A subject who has become tolerant to MDMA will still respond to MDA and vice versa. Finally, there is the matter of the isomers. The recemic mixture of R and S isomers typically prepared by the chemist can be separated into the R and S isomers. With MDMA the S isomer seems to be 4 times as active as the R isomer. In the case of MDA, the R isomer is more active than the S. This is an extraordinarily interesting finding that requires confirmation because it may imply that the central nervous system's receptors on which these compounds work are different in structure and in location within the brain. Thus, there is some evidence that MDA works primarily on dopamine receptor systems while MDMA may work on serotonin receptor systems. The point to this summary is that it is scientifically hazardous to extrapolate from a similarity in chemical structure to a presumed pharmacological identity. An N-methyl group can make a very big difference.

2. <u>The DEA states that MDMA has no legitimate medical use</u>. Superficially, this is true because the anecdotally reported usefulness of MDMA by several well trained and serious clinical investigators has not received the blessing of legitmacy. I am not at all sure how one goes about legitimizing a drug that is not patentable and hence which lacks the funds of the quantity that drug companies employ to put their drugs on the market. The fact remains that several clinicians have used MDMA and Dr. George Greer of New Mexico, has reported extensively on it. He has limited his work to the study of its effects on subjects who are physically healthy and who have no history of a socially or vocationally disabling psychological condition other than alcohol or drug intoxication. Thus all of his subjects were

either neurotic or had adjustment reactions which made them unhappy. In this group of 40 patients, he found that the drug enhanced communication between people involved in significant emotional relationships, it also enhanced introspection, frequently with the achievement of insight, it improved self image, and apparently, it facilitated psychotherapy. It should be granted that Dr. Greer's work remains anecdotal even though approximately 50 subjects have been treated. To this number may be added unpublished reports from approximately 6 other psychiatrists who have employed the drug in similar settings. It is also worth noting that Greer and others report that the immediate effects are shortlasting, that larger doses diminish the pleasurable effects and increase the distressing side effects, that repeated daily use leads to tolerance for the desirable psychological effects without effecting the undesirable side effects and that no one in their experience has elected to take MDMA more than once a week and usually much less because the psychological "glow" of the initial treatment is long lasting.

I think it important that MDMA be tested against other stimulants in a double blind fashion in order to eliminate or minimize the mystical and charismatic placebo effects. I would recommend double blind studies be conducted comparing MDMA not to an inactive placebo but rather to active placebos, like methylphenidate or fenfluramine.

Although one should research this drug very cautiously, its reported mechanism of action suggests that it might have clinical utility in several other serious psychiatric conditions for which treatment is currently not very effective. Thus, in schizophrenia the so-called positive symptoms (things which are there but shouldn't be) like hallucinations and delusions respond very well to the traditional antipsychotics, but the negative symptoms (things which are not there but should be) like autistic behavior, inability to communicate and to feel affect or empathy, do not respond to the typical neuroleptics. Recent work involves giving two drugs simultaneously, one to reduce the positive symptoms and the other the negative symptoms. MDMA in a controlled clinical trial warrants testing for the treatment of negative symptoms in such patients. Childhood autism is an essentially untreatable condition in which the child is unable to relate to significant people in his environment. MDMA might be tried on such children, partly because this distressing illness is otherwise untreatable and partly because the reported effects of enhancing communication among adults might be helpful in autism. Posttraumatic stress disorder is another condition that might warrant a trial. In World War II abreaction with barbiturates was used effectively to free the inhibited terror of soldiers following severe stress. There is some evidence that in posttraumatic stress disorder abreaction in

a congenial environment might be helpful. MDMA as a communication enhancer might be worth a trial. I have mentioned previously that the treatment of choice today for hyperactivity and learning disability is methylphenidate or dextoamphetamine. MDMA, it could be argued, has properties sufficiently similar to those compounds to warrant a trial. Fenfluramine has been introduced and is an accepted treatment for obesity. A recent report suggests that it may also be useful in the treatment of childhood autism. Some similarity between the actions of fenfluramine and MDMA might warrant trials of the use of MDMA in eating disorders and in childhood autism. Finally, as far back as Freud and many times in the intervening 70 years, agents have appeared which it was proposed would enhance insight oriented psychotherapy. In principle, there is no reason why such drugs should not exist. In practice, LSD, mescaline, and similar drugs have failed to be consistently useful. The search for such drugs should go on and someday they will be found. MDMA might be such a drug. I should close this section by noting that cocaine abuse has become a major national health problem with tremendous economic implications. A legitimate synthetic substitute for cocaine is badly needed. At least one verbal report states that a daily cocaine user who experienced MDMA stopped cocaine and took MDMA at two-weekly intervals instead. If this is true, and can be confirmed, MDMA would have enormous value for cocaine abuse. Let me close this section by agreeing that today MDMA has no "legitimate" use but there are many reports from reliable clinicians that it is a useful drug and further study might legitimatize it. I suggest that it deserves thorough investigation for the claimed uses today and for the potential future uses that I have outlined above.

3. <u>The DEA states that MDMA produces stimulant and psychotomimetic effects</u> similar to those produced by MDA but at slightly higher doses. This is, again, a partial truth. There seems to be no doubt that MDMA has stimulant effects like all other amphetamines. The psychotomimetic effects are not similar either quantitatively or qualitatively. Indeed, there is some question whether MDMA produces any psychotomimetic effects. To the best of my knowledge, active hallucinations have not been noted with MDMA. MDA has been reported to occasionally produce hallucinations in large doses but even MDA is a much weaker hallucinogen than mescaline to which it is closely related in chemical structure. This again emphasizes the difficulties in projecting human clinical effects from comparisons of chemical structure or from testing in lower animals. Human tests, under rigorously controlled conditions, are necessary.

4. <u>MDMA is easy to synthesize clandestinally</u>. I agree and I suspect that given its recent publicity in magazines and

television, it will continue to be produced. The seductiveness of the mystique of its benefits cannot be overemphasized. I have had phone calls from psychiatrists, psychologists, attorneys, educators, and biomedical scientists who recommend it or who wish to try it. Rather than make research difficult, I think it imperative to conduct research that will give an honest evaluation of its risks and benefits.

5.& 6. MDMA has been found in illicit traffic throughout the United States. I agree. It has also been reported to be associated with medical emergencies and one death reported by Dawn. I can only comment that the gas chromatographic, high pressure liquid chromatographic and mass spectrometric methods for the detection and measurement of MDMA require sophisticated laboratories and analytical chemists. Since clandestine laboratories rarely make pure material, it would be simple to misidentify MDMA or for that matter to miss it when it is present in tissue fluids. The case of death reported by Dawn in Seattle has been questioned legitimately by Shulgin. I would remain somewhat suspicious of the other reports on toxicity or for that matter of the nature of the materials found on seizure. I should say in passing that if MDMA is as widely produced and distributed as the DEA implies and if its abuse is as great as that which the DEA implies, it is most surprising that only one death has been reported and this one is questionable. It remains possible that many more deaths have occurred that have not been identified, but it is equally possible that MDMA is singularly nontoxic nor subject to abuse. These are research questions.

I wish to emphasize that I am not an advocate of MDMA nor an opponent. From what I have read, it is an interesting compound which deserves further rigorous controlled study. I would hope that the FDA and the DEA will take actions to expedite such research rather than to inhibit it. I think this is best done by making it a Schedule III drug.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on April 24, 1985.

Morris A. Lipton

Morris A. Lipton, Ph.D., M.D.
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STATEMENT FOR DEA AND FDA HEARINGS ON MDMA

by

Lester Grinspoon, M.D.

"The rejection of any source of evidence is always treason to that ultimate rationalism which urges forward science and philosophy alike." (Whitehead).

Between 1950 and the mid 1960s there was a robust interest in the possibility that LSD and related drugs (sometimes called "hallucinogenic" or "psychedelic") might be therapeutically useful for psychiatry. There were more than a thousand clinical papers discussing forty thousand patients, several dozen books and six international conferences on therapy using these drugs. The subject aroused the interest of many psychiatrists who were in no sense cultural rebels. The use of LSD and related drugs was recommended for a wide variety of problems, including alcoholism, obsessional neurosis, and the treatment of the dying. Almost all publication and most therapeutic practice in this field have come to an end, as much because of legal and financial obstacles as because of the loss

of interest. Experimental efforts were abandoned before the degree of success or failure was adequately determined. It would be wise to see whether we can salvage something from those two decades of research and clinical practice rather than write them off as a mistake that now has only historical interest. If the therapeutic results have seemed erratic and inconsistent, that is partly because of the complexity of the effects of these drugs. For the same reason we may simply not yet have had enough time to sort out their best uses. In rejecting the absurd notion promoted by some that these drugs were a panacea, we have chosen to treat them as entirely worthless and extraordinarily dangerous. The time has come to find an intermediate position.

It is interesting that several cultures in the western hemisphere make religious or therapeutic use of certain drugs which are banned by the United States federal and state governments. This is true especially in the western United States and Mexico. We have made a curiously self-disparaging decision when we judge that no one in a modern industrial society is qualified to do what is done by a leader of the peyote ceremony in the Native American Church or a Mazatec Indian healer who uses mind-altering mushrooms. It has even been recognized in federal alcoholism clinics for Indians that peyote may have

some value.

There are now several new drugs which may have therapeutic interest and may also be significant for the study of the human mind. Undoubtedly there will be more such drugs synthesized in the future. The effects of these drugs are sometimes different from those of LSD and other familiar substances, and the differences may be highly significant. We cannot analyze these questions properly without more controlled human research.

The drug of central interest here is 3,4-methylenedioxymethamphetamine (MDMA). When taken in doses of 75 to 150 mg orally, this phenylalkylamine seems to have a remarkable capacity to help people to get in touch with feelings, to become more open and trusting and less defensive, to facilitate the recall of early memories, and to invite self-exploration and insight. Unlike LSD and drugs with similar effects, it does not ordinarily produce perceptual distortions, body image change, or changes in the sense of self. Although MDMA is chemically related to methylenedioxy-amphetamine (MDA), it is a milder and shorter-acting drug with less consciousness change and fewer secondary neurological symptoms. Adverse sequelae seem to be rare, although not unknown. In short, MDMA appears to have some of the advantages of the LSD-like drugs without most of the corresponding disadvantages.

This drug is now being taken by growing numbers of people, particularly students and young professionals. It has already been used for therapeutic purposes by a number of physicians and psychotherapists. We have had discussions with several mental health professionals who have found it useful as a catalyst of self-exploration. The users are increasingly seeking people who know how to employ MDMA in a therapeutic setting. MDMA might be useful in marital counseling, in diagnostic interviews, in helping patients decide whether they want to go through the process of psychotherapy, in helping psychiatrists decide whether a patient can benefit from the kind of insights that psychotherapy provides, and possibly as an occasional catalyst of the insight-oriented psychotherapeutic process. Whether this turns out to be true or not can be learned only by more systematic human research, preceded by necessary animal toxicity studies. The kind of informal research that is going on now will not suffice for an accurate assessment of either its therapeutic potential or its toxicity or abuse potential. Prematurely discouraging more systematic research by putting MDMA in Schedule I of the Controlled Substance Act would be a mistake.

I have been involved in the study of psychoactive drugs since 1967. I have published a number of papers

and six books in this area. Two of the books have direct relevance to this subject (Psychedelic Drugs Reconsidered. Lester Grinspoon and James B. Bakalar, New York: Basic Books, 1979 and Psychedelic Reflections. Lester Grinspoon and B. James Bakalar, New York: Human Sciences Press, 1983). During the course of this work I have read widely in the scientific literature on the subject and have accumulated much experience with people who use various psychoactive drugs.

Although our understanding of MDMA is at this time inchoate, I think that its potential for abuse is probably low, if one defines abuse as involving harm to the individual and/or society. At any rate, a high abuse potential has not been demonstrated and current reports indicate relatively few serious problems. Because of the nature of the experience users generally do not wish to repeat it frequently or treat it casually and recreationally. For similar reasons I believe that its dependence producing potential is low. In addition I have heard of no reports of craving or withdrawal symptoms. There do not seem to be any effects so disturbing, disorienting or physically dangerous that it would be impossible for MDMA to be used safely under a physicians's supervision. It is reported to have been used hundreds of times in psychotherapy with few serious complications.

Research would help us to determine how to prevent any such complications.

My background and experience in this area are set forth in the accompanying curriculum vitae.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on April 18, 1985

Lester Grinspoon MD

Lester Grinspoon, M.D.

UNITED STATES DEPARTMENT OF JUSTICE
DRUG ENFORCEMENT ADMINISTRATION

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

STATE OF NEW JERSEY)
) ss:
COUNTY OF ESSEX)

Statement of Zofia Dziewanowska, M.D., Ph.D.

Zofia Dziewanowska, M.D., Ph.D., being first duly sworn, deposes and says:

1. My name is Zofia Dziewanowska, M.D., Ph.D.

2. I am currently employed by Hoffmann-La Roche Inc. (Roche) in the capacity of Director of Clinical Research and Assistant Vice President.

3. My curriculum vitae is attached.

4. I have been employed by Roche since 1976 and during that time have been involved in the direction of medical research on investigational drugs. I have also been involved in drug research for Merck Inc. International Division from 1972 to 1976.

5. I have been asked to address the question as to what constitutes "currently accepted medical use in treatment in the United States." It is my professional scientific opinion that substances which are the subject of Investigational New Drug Exemptions (IND) and even substances at the pre-IND stage of development must be considered as belonging to the category of substances having "currently accepted medical use in treatment in the United States" as that phrase is used in the Federal Controlled Substances Act, since they have the potentiality for becoming approved drugs. Such substances have the potentiality for receiving approved New Drug Applications (NDA) from the FDA. All substances must pass through the pre-IND and IND stages of development prior to final approval. This potentiality for medical use must be considered a critical

factor in determining what constitutes "accepted medical use in treatment in the United States."

6. IND substances are considered to have a therapeutic potential, and may be useful for more than merely the clinical data obtained as a result of their administration. To illustrate this point, many substances under investigation are being used on a "compassionate plea" basis in patients for whom no other therapy exists. Because such substances are medically essential to the well-being of certain patients, they may be provided to such patients on an emergency basis for therapeutic purposes, even without NDAs.

7. Inappropriate early regulation of substances under the Controlled Substances Act would have a chilling effect upon the pharmaceutical research process.

8. If an investigational substance were to be placed in Schedule I, it is my understanding that a Schedule I registration would have to be obtained. A separate detailed Protocol for each Schedule I substance would have to accompany the registration application. Moreover, any change or addition to the Protocol would be subject to a formal amendment. It is my understanding that the registration application process could take as long as 6-8 months.

9. If an investigational substance is placed in Schedule I, individual physician-investigators studying the substance would need to seek separate DEA registrations. Although most physicians possess DEA registrations to prescribe controlled substances, they would not possess Schedule I research registrations. Moreover, such investigators would need to seek individual state controlled substance registrations.

10. It is my understanding that substances that are placed in Schedule I cannot be transferred without official order forms. This order form requirement for all transfers of investigational substances whether to physicians or others represents another burdensome procedure on the research process.

11. If an investigational substance were to be scheduled under the Controlled Substances Act, that substance would be subject to highly detailed inventory and accountability requirements, necessitating the expenditure of additional time, and the generation of additional paperwork during the various steps in the research function on the part of physician investigators as well as the company. Additionally, these substances would be subject to the security controls associated with controlled substances.

12. The time delays and increased administrative work of this nature would discourage incentive for pursuing research on such a substance. I agree that scheduling of substances with abuse potential is an important and necessary process. I also recognize that, in recent years, the government has in certain instances attempted to make it easier for researchers to obtain Schedule I registrations. Nevertheless, scheduling substances, particularly in Schedule I, during the investigational phases of pharmaceutical development would substantially slow down the development process, and would definitely inhibit a company's incentive to invest in research on many potentially important substances, thereby affecting negatively the development process.

13. The fact that a substance has been placed in Schedule I of the Controlled Substances Act may very well need to be included in the patient consent form which, under Federal Food and Drug Administration regulations, must be signed by patients administered investigational drugs pursuant to an IND. This requirement could have a chilling effect upon patient recruitment for important substance studies, and could needlessly frighten potential volunteers who may be lead to believe, because of the Schedule I treatment, that a substance has greater abuse potential than it actually does. Because the Schedule I treatment is only an "interim" placement until the substance is approved, in reality, the Schedule I classification is actually a "misclassification."

14. Clearly, upon approval of the investigational drug, which, during the investigational period has been placed in Schedule I, a descheduling or rescheduling process must take place, resulting in additional paperwork, potential hearings, and substantial time delays. Since it is my understanding that state legislatures and administrative agencies typically schedule substances in accordance with the federal schedules, such rescheduling must also take place on an individual state-by-state basis, resulting in an even greater expenditure of time (often over one year) and resources. Assuming the rescheduling or descheduling at the state and federal levels does not become effective immediately upon approval of the substance, there could be a substantial delay in the actual marketing of a potentially important therapeutic substance.

15. In any event, it is my understanding that a substance cannot be placed in Schedule I unless it possesses a "high" potential for abuse. Unless an investigational substance has been shown to have such a high abuse potential, placement of the substance in Schedule I would be inappropriate.

16. The added expenditure of time, paperwork and administrative delays for a pharmaceutical company caused by the inclusion of an investigational substance in Schedule I would result in significant increased economic costs associated with the cost of research. These additional financial costs and time delays would constitute a major disincentive to a pharmaceutical company to pursue the development of many potentially important drugs. Costs and time are a key factor in a pharmaceutical company's determination as to whether to commit itself to a particular area of research. The increased costs of research associated with the imposition of Schedule I controls upon an investigational substance would have a deterrent effect upon pursuit of research of new promising drugs.

15. Therefore, in my opinion, in order to avoid inappropriate scheduling actions which would negatively affect the development of needed pharmaceuticals, the phrase "currently accepted medical use in treatment in the United States" should be understood to include IND substances and those pre-IND substances whose pharmacological and other scientific profiles would lead to the conclusion that they may receive NDAs in the future or may be otherwise used therapeutically.

Zofia Dziewanowska, M.D., Ph.D.

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340 Kingsland Street
Nutley, New Jersey 07110

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Sworn to and subscribed before me
this 22nd day of April 1985.

Joyce S. McGuire

JOYCE S. McGUIRE
NOTARY PUBLIC OF NEW JERSEY
MY COMMISSION Expires Nov. 16, 1989

Rodney A. Houghton, M.D.
Star Route #330
Placitas, NM 87043

Mr. Richard Cotton
1775 Pennsylvania Avenue, N.W.
Washington, D.C. 20006

Dear Mr. Cotton:

In this ~~this~~ testimony, I will address the issue of the use of MDMA as an accepted and safe medical treatment in the psychiatric practice of Dr. George Greer, M.D., based on my training, experience, and knowledge in this matter.

I am a Medical Doctor licenced to practice in my subspeciality as a Psychiatrist in the State of New Mexico. I trained as an undergraduate at Texas Tech University where I graduated with honors receiving a Bachelor of Science in Zoology. I attended Medical School at the University of Texas Health Science Center at San Antonio, receiving my M.D. Degree in 1976. I then moved to New mexico to further my subspeciality training in Psychiatry at the University of New Mexico Department of Psychiatry. I finished this program in 1980, serving as Chief Resident my final year, and embarked on a career as a Community Psychiatrist. As Medical Director of Sandoval County Human Services, Inc., a post I held for five years, I developed a program to provide mental health care to the people of a rural county in New Mexico. I also conducted psychiatric clinics in three other rural counties. For all these counties I was the only psychiatrist locally available and in the course of this work, have treated hundreds of patients of all ages and of all socio-economic and racial backgrounds. I was also instrumental in developing the non-profit Community

Mental Health programs in these counties, funded by the Department of Health and Environment of the State of New Mexico. In 1983, I acted as the expert on psychiatric care in testimony to the Department concerning the State Mental Health Programs, the needs of these programs in terms of funding and man power, and the direction the State should take in relation to providing quality psychiatric treatment in rural New Mexico counties. In the Community Programs with which I consulted, I trained and supervised Masters level therapists in providing individual, groups, and family therapy for their clients. I also evaluated patients for medication and hospitalization and treated them as required with pharmacotherapy, individual, groups and family therapy, and testified as expert witness in court for committment hearings. I also provided in-service training on various aspects of clinical psychiatry to the communities in which I worked, drawing participants from social service agencies, general hospital staff including nurses and emergency room personnel, law enforcement agencies including policemen, jailors, and the local sheriffs.
In addition to this work as a Community Psychiatrist, I have been medical consultant to the department of Health and Human Services, Social Security Administration, reviewing psychiatric disability cases for the Disability Determination Unit of New Mexico, to determine medical evidence for disability compensation and whether applicants should receive compensation based on standards developed by the Social Security Administration. I am also a member of the Education, Training, and Service Committee of the Human Resource Development Program, Mental Health Bureau.

This committee reports to the State Bureau responsible for funding and maintaining standards for Community Mental Health programs, and provides input concerning manpower issues in mental health throughout the State. I am a Clinical Assistant Professor of the University of New Mexico Department of Psychiatry, a General Member of the American Psychiatric Association and the New Mexico Psychiatric Association.

I am currently in the process of changing the direction of my career to a focus on Private Psychiatric Practice. Since July 1984, I have been a member of the Medical Staff at Vista Sandia Psychiatric Hospital in Albuquerque, the oldest and largest private in-patient facility in New Mexico, and have a busy in-patient and out-patient practice. I serve as Chairman of the Therapeutics Committee, establishing standards of psychiatric care in this not-for-profit psychiatric hospital. I also regularly provide training to community lay people and para-professionals, nurses and mental health workers through this hospital's Community Education and Research Department.

In addition, I am a member of the Medical Staff of Heights Psychiatric Hospital in Albuquerque, a recently established facility, where I am a member of the Therapeutics Committee and the Adult/Young Adult program committee. I am focusing on the treatment of seriously disturbed adolescents in an in-patient setting here.

In summary, during the nine years of practicing Psychiatry in New Mexico, I have become well acquainted with the Acedemic Community Rural and Private Practice Standards of Psychiatric evaluation and treatment. I have been involved at all levels

of developing and maintaining quality medical treatment of psychiatric patients in this State -- in the political and government agency area, in the grass roots community level and in the private profitable and not-for-profit hospitals.

I have as friends, teachers, and colleages, psychiatrists from the University setting, including Dr. Robert Kellner, M.D., Ph.D., Professor and Vice Chairman and Director of Research for the Department of Psychiatry. He is a well known clinical researcher publishing many papers in the field of psychopharmacology. We have consulted on cases and he has supervised me on a research case study involving the use of the investigational drug Pimozide. From this association I became familiar with research criteria, protocols, and ethical issues involving humans in research. This training and experience have provided me with a sound basis for serving as a member of Dr. Greer's Peer Review Committee for his research into the clinical uses of MDMA. I have been involved with him since he began the study as a consultant reviewing and offering suggestions on his protocol, informed consent forms, patient selection, and the before and after session questionairre. I also participated as a subject in his research with MDMA from which he wrote the paper "MDMA, A New Psychotropic Compound and Its Effects in Humans". I am consequently, totally familiar with Dr. Greer's use of MDMA in his research and personally familiar with its effects as prescribed under Dr. Greer's medical supervision.

In my expert opinion, as one who is familiar with the accepted standards of Psychiatric Practice in New Mexico, indeed, having

established many of those standards for five rural communities and Community Programs throughout the State, I believe Dr. Greer's use of MDMA is an accepted and safe medical practice. I base this opinion not only on my own experience and what I believe to be acceptable, but also on my conversations with teachers and colleagues about his work. I also judge that Dr. Greer's research design for studying MDMA is sound and follows the basic rules of scientific observation and documentation. His work with patients has shown the safety of the MDMA therapy as well as the positive benefits which can be derived from its use under strict medical supervision.

I declare under penalty of perjury under the laws of the United States of America that the forgoing is true and correct. Executed on this 29th day of April 1985 in Placitas, New Mexico.

Rodney A. Houghton, M.D.

WILL L. MacHENDRIE, M.D.
General Psychiatry
1418 LUISA STREET, No. 4
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Telephone 984-1687

30 April 1985

Mr. Richard Cotton
Dewey- Balantine
1775 Penn Avenue N.W.
Washington, D.C. 20006

Rebutal Testimony of Will L MacHendrie, MD in the DEA hearing on scheduling of MDMA under the Controlled Substance Act.

Dear Committee Members,

I am a Board Certified psychiatrist and for the past five years I have been working in community mental health and private practice in New Mexico.

For the past two and one half years, I have been on the Peer Review Committee for Dr. George Greer's use of MDMA. In that capacity, I have extensively reviewed his methodology and his results regarding the therapeutic use of MDMA. I feel that there is definitely a medically accepted use of this drug in treatment and that there is acceptable safety for use under medical supervision.

I declare under penalty of purgery under the laws of the United States of America that the forgoing is true and correct and executed on April 30, 1985 in Santa Fe, New Mexico.

Respectfully,

Will L MacHendrie M.D.

Will L. MacHendrie MD

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CURRICULUM VITAE

Name: Will L. MacHendrie, M.D.

Birth Date: June 15, 1940
Trinidad, Colorado

Marital Status: Married

Medical Licenses In:
New Mexico, #80-60

Diplomate:
American Board of Psychiatry and
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EDUCATION

1964-1967 Pre-Med. University of Colorado, Boulder Colorado

1967-1971 Doctor of Medicine, University of Colorado, Denver, Colorado
(Externship, Santa Domingo Pueblo)

1971-1972 Internship, Gorgas Hospital, Canal Zone
(Multi-Cultural Experience)

1972-1975 Psychiatric Residency, University of California - Davis,
Sacramento, California
(Community Mental Health Orientation)

PROFESSIONAL EXPERIENCE

6/75-5/77 Assistant Clinical Professor of Psychiatry, University of California - Davis. Inpatient and outpatient, direct clinical services in a community mental health orientated program. All therepeutic modes. Supervisor for psychiatric residents and psychiatric clerkship for medical students in our clinic.

7/77-12/79 Chief of Clinical Services, Sierra County Mental Health Program, Sierra County, California. In charge of all inpatient and outpatient care; individual, group and family therapy. Medical liason consultation and biofeedback. Supervision of psychiatric social workers and community mental health workers in rural setting.

1/80-4/80 Staff Psychiatrist at Hutchings Psychiatric Center, Syracuse, New York. Temporary position to coordinate treatment planning and supervision for a model geriatric inpatient unit.

Professional Experience continued

7/80-7/83 Staff Psychiatrist for Sangre de Cristo Mental Health Service in three Northern New Mexican counties; Taos, Colfax and Los Alamos. Direct clinical and supervisory responsibilities with members of the Anglo, Hispanic and Indian communities. Inpatient and Emergency Room responsibilities at St. Vincent Hospital in Santa Fe, New Mexico.

7/83-present Private practice in Santa Fe, New Mexico. Consulting psychiatrist for Los Alamos Family Council (a community mental health clinic). Active staff for St. Vincent Hospital. Consulting staff for the Los Alamos Medical Center.

PROFESSIONAL ORGANIZATIONS

1972-present American Psychiatric Association

1972-1980 Central California Psychiatric Society

1980-present New Mexico Psychiatric Society

UNITED STATES DEPARTMENT OF JUSTICE

DRUG ENFORCEMENT ADMINISTRATION

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

DIRECT TESTIMONY OF FRANK L. SAPIENZA, M.S.

I, Frank L. Sapienza, make the following statement:

I am a chemist employed at the Drug Control Section, Office of Diversion Control, United States Drug Enforcement Administration (DEA). I received my undergraduate and graduate degrees in chemistry from the University of Pittsburgh. I received my masters degree in 1972. Prior to my current position with the Drug Control Section at DEA, I was a forensic analytical chemist at the United States Army Criminal Investigation Laboratories in Fort Gordon, Georgia and Frankfurt, Germany (1970-71), at the Allegheny County Crime Laboratory (1971-72) and at the DEA Mid-Atlantic Laboratory (1972-78). I have worked in the Drug Control Section of DEA since 1978.

In my current position with the Drug Control Section, I am responsible for reviewing and evaluating information relevant to the actual or potential abuse of substances. I prepare reports on the substances reviewed which then serve as the basis for recommendations and decisions concerning the classification and scheduling of substances under the Controlled Substances Act (CSA). I review information from the world scientific literature, from sources within DEA as well as from other Federal, state and local data sources. I have conducted reviews of

narcotic, stimulant, depressant and hallucinogenic substances relative to both domestic and international scheduling.

Reports from DEA agents that clandestine laboratory operators were producing an analog of MDA in an effort to circumvent the CSA, forensic laboratory reports of this substance in the drug traffic, and requests from state and local officials to examine the possibility of controlling this MDA analog prompted DEA to initiate a drug review of the substance, 3,4-methylenedioxymethamphetamine (MDMA).

After gathering and reviewing the available data concerning MDMA I prepared a document entitled "Schedule I Control Recommendation Under the CSA for 3,4-Methylenedioxymethamphetamine (MDMA)" in January, 1984. (Government document B-2) This document contains an analysis of the factors listed in 21 U.S.C. 811(c) relevant to placing MDMA under CSA control. It also contains an evaluation of the criteria necessary for placing MDMA into Schedule I of the CSA. The document was provided to the Department of Health and Human Services on March 3, 1984 for a scientific and medical evaluation and scheduling recommendation for MDMA.

I examined a number of data sources within DEA in conducting my review of MDMA. STRIDE (System to Retrieve Information from Drug Evidence), is a system which collects, stores, processes and retrieves laboratory analysis information from drug evidence samples submitted to DEA laboratories. Most of the evidence submitted to DEA laboratories is obtained in the course of criminal investigations. The appearance of a substance in STRIDE is a good indication that the substance is a part of the illicit drug traffic. STRIDE data is drug specific and the substances found are verified by chemical analysis, and thus STRIDE is an extremely reliable qualitative measure of the involvement of a particular

substance in the illicit drug traffic. Since law enforcement priorities and the control status of substances play a major role in determining the nature and the direction of criminal investigations, STRIDE data provides a somewhat biased view of the quantitative measure of a substance's appearance in the illicit drug traffic. Most of DEA's enforcement efforts are directed at major distributors of Schedule I and II substances and not at individuals distributing noncontrolled substances. Furthermore, if an agent obtains a purported controlled substance (MDA) which upon chemical analysis is found to be a noncontrolled substance (MDMA), the investigation will usually be terminated. Thus, noncontrolled substances such as MDMA are underreported in STRIDE.

Another DEA source of information is the clandestine laboratory report which describes either operating or potential laboratories having the necessary chemicals and equipment to produce a controlled substance. Ocassionally, criminal investigators will find a clandestine laboratory suspected of producing a controlled substance but the analysis of materials obtained from the laboratory, indicate that a noncontrolled substance is being produced. Investigators may terminate surveillance of clandestine laboratories once it is determined that only noncontrolled substances are being produced. Clandestine laboratories producing only noncontrolled substances are sometimes seized if the agents believe that controlled substances are being manufactured. This explains why DEA has seized laboratories making MDMA. Other DEA data sources include investigative case files which describe the circumstances surrounding the submission of drug evidence to DEA laboratories, intelligence reports

concerning the appearance of new drugs on the illicit market and their trafficking and abuse patterns, and general information contained in DEA files regarding the substance in question.

Non-federal forensic laboratories will sometimes voluntarily report unusual drug exhibits or new drugs of abuse to DEA. Additionally DEA queried some of these laboratories in an attempt to determine if MDMA is encountered in the drug traffic. As with STRIDE, this data is highly reliable as a qualitative indicator of the street availability of a substance. Many forensic laboratories do not identify or report noncontrolled substances, therefore, noncontrolled substances are underreported by these laboratories.

The Drug Abuse Warning Network (DAWN) provides information on the abuse of substances through the collection of data on the number of emergency room visits and deaths associated with a substance. DAWN emergency room data is not verified by chemical analysis and thus in the case of illicit preparations, may not be an accurate indicator of the number or nature of emergency room visits actually associated with a substance. MDMA is trafficked on the street as MDA, MMDA, ADAM, etc. and it is likely that some DAWN mentions attributed to these and other substances may be due to MDMA.

My review of the scientific and medical literature and the above data sources as well as others provides the following description of MDMA:

MDMA is the N-methyl analog of MDA and it is in the chemical class of compounds known as ring-substituted phenylalkylamines. MDMA differs from MDA structurally in the same way that methamphetamine differs from amphetamine, by the addition of an N-methyl group. Other ring-substituted phenylalkylamines include the substances, 3,4,5-trimethoxyamphetamine (TMA), 4-methyl-2,5-dimethoxyamphetamine (STP), 4-bromo-2,5-dimethoxy-amphetamine (DOB), para-methoxyamphetamine (PMA) and 3-methoxy-4,5-methylenedioxyamphetamine (MMDA). All of these substances have a high potential for abuse, no accepted medical use and are classified as hallucinogens in Schedule I of the CSA.

The scientific literature shows that the pharmacological profiles of MDMA and MDA in animals are similar. Both of these substances and mescaline produce the same signs related to motor, autonomic and central nervous system function in the unanesthesized dog and monkey. MDMA and MDA produce analgesia in mice using stretch, hot-plate and tail-flick tests. Increased motor activity in mice was observed after administration of both MDA and MDMA. In humans the effects of MDMA were reported to be similar to those of marihuana, psilocybin and MDA. At low doses both MDA and MDMA produce a change in consciousness without hallucinations, increases in tactile, visual and acoustic sensory perceptions, a decrease in tension and a mood lightening effect. Physical symptoms reported were jaw clenching, mydriasis, pulse acceleration and anxiety produced nausea.

My review of the scientific literature failed to identify any references to studies concerning the therapeutic utility of MDMA. A

check with the Food and Drug Administration revealed that there are no investigational new drug applications or approvals for MDMA. There is also no indication from the chemical literature and chemical manufacturing sources that there is a commercial manufacturer of MDMA.

My review shows that MDMA has been encountered with increasing frequency in the illicit drug traffic since 1970. DEA laboratories analyzed over 60,000 dosage units of MDMA in 34 exhibits from 12 states between 1972 and 1983. MDMA exhibits were found in California, Illinois, Washington, D.C., Colorado, Tennessee, Florida, New York, Pennsylvania, Alabama, Louisiana, North Carolina and Oregon. Non-federal forensic laboratories have reported the analysis of at least 41 MDMA evidence samples to DEA since 1978. The states reporting MDMA submissions were Oregon, Texas, Virginia, California, North Carolina, New York, Maryland and Tennessee. MDMA is trafficked as MDA, Ecstasy, XTC, ADAM, MDM or MDMA. Laboratory submissions range from 1 dosage unit to over 2 kilogram samples in capsules and powders. Investigative case files show that MDMA has been distributed by individuals also distributing controlled substances including cocaine, marihuana, MDA, methamphetamine and PCP.

MDMA is produced in clandestine laboratories by procedures analogous to those used to produce MDA, amphetamine and methamphetamine. The 2 synthetic routes used to produce MDA or MDMA yield the racemic mixture. In those samples of MDA and MDMA for which optical isomerism was determined by DEA laboratories, the racemic forms were found in each instance. MDMA can be synthesized from readily available substances by individuals with minimal chemical education or training.

DEA has encountered 3 functioning MDMA laboratories and 1 non-operational laboratory with the chemicals necessary to produce MDMA. These laboratories were located in Tennessee, California, Georgia and Florida and were capable of producing kilogram quantities of MDMA on a routine basis. Additional MDMA laboratories have been identified by DEA agents but not investigated due to the noncontrolled status of MDMA. Both DEA laboratories and PharmChem Laboratories indicate the presence of inpurities in many of the MDMA samples analyzed. Information from clandestine laboratory investigators indicates that MDMA is being produced in an effort to produce a substance with MDA-like effects but not controlled under the CSA. PharmChem Laboratories, an anonymous testing laboratory in California has consistently reported submissions of MDMA since at least 1976. They group MDA and MDMA together and consider both to be drugs of abuse.

My review showed that MDMA has been associated with medical emergencies as evidenced by the 8 DAWN emergency room episodes between January 1, 1977 and April 1, 1981. The reports were from California, Illinois and Massachusetts. A death associated with the use of MDMA was reported in DAWN from Seattle, Washington in 1979. Since DAWN data is not routinely chemically verified and since MDA and MDMA may be used interchangeably, it is likely that some DAWN emergency room mentions attributed to MDA as well as other substances may in fact be due to MDMA. The toxicology reports listed MDA in these cases; MDMA was incorrectly reported on the DAWN forms.

Police reports of individuals who have used a substance identified by laboratory analysis as MDMA show that these individuals exhibited intoxication and paranoid behavior after MDMA use.

Since completing my review of MDMA I have continued to collect information relative to the abuse of MDMA. Since 1984 DEA laboratories have analyzed an additional 7 exhibits of MDMA from Texas and California; 4 of the exhibits were obtained since January, 1985. MDMA is now available in tablet form as evidenced by submissions from both Texas and California. The tablets appear to be clandestinely produced, contain 110 mg of racemic MDMA and are sold as Ecstasy. The price of the tablets in Texas is $20 per dosage unit. In September, 1983, a clandestine laboratory with sufficient material to make over 1 kilogram of MDMA was seized by DEA. Forensic laboratories in Texas, Massachusetts, Oregon and California report analyzing samples containing MDMA. One of the MDMA exhibits from Texas was submitted to the Jefferson County Crime Laboratory by a newspaper reporter who obtained the tablet of MDMA at a party set up to promote the use and distribution of "Ecstasy." Another exhibit was submitted to the Los Angeles Police Department Laboratory by a physician who stated that MDMA was readily available in Los Angeles and abuse among young people was prevalent.

Individuals promoting the distribution and street use of Ecstasy are circulating pamphlets and flyers describing MDMA, how to experience it most effectively and how to compensate for difficult experiences with MDMA. These pamphlets are attached as Exhibits 1 through 5. The The material makes no mention of the use of MDMA in a medically supervised environment. It warns of "very difficult trips," "negative reactions," "a narrow effective dosage doorway. . . .

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If too much is taken, it becomes toxic," "headaches cramps and acute fatigue if repeated too frequently," "great care must be taken in swallowing solid food since there is a minimum amount of anesthesia present." Ecstasy is described as "the ultimate high," "a good trip," "a powerful, pleasurable and peaceful experience but it's also quite demanding," "a two day trip," and a substance that "the government hasn't made illegal yet."

Published descriptions of the effects of MDA on humans by users and researchers parallel those claimed by the pamphlets and circulars promoting MDMA. (Attached as Exhibit 6) The April, 1985 issue of "High Times" in a report on MDA prepared by David Smith, M.D. and Rick Seymour of the Haight-Ashbury Free Medical Clinic states that "Some researchers (Grinspoon and Bakalar) have concluded that MDA produces feelings of aesthetic delight, empathy, serenity, joy, insight, and self-awareness, without perceptual changes, loss of control or depersonalization; and seems to eliminate anxiety and defensiveness." (Attached as Exhibit 7) The same issue of High Times magazine, lists the prices for MDMA in Austin, Texas and Boulder, Colorado (Attached as Exhibit 8) while the January and February, 1985 issues of High Times list the prices of MDMA on the United States national market. (Government document B-11) Other substances with price quotes in High Times include marihuana, LSD, cocaine, psilocyben mushrooms, and hashish.

Toxicology Testing Service, an anonymous testing laboratory located in Miami, Florida reported 19 submissions of MDMA since April, 1984; 12 of these since October, 1984. Submissions were from Florida, New York, California, Texas, Oregon, Vermont, New Hampshire, and Washington, D.C.

MDMA was submitted in powder, capsule and tablet form as MDMA, MDA, MDM, Ecstasy, ADAM, XTC, cocaine and Essence. Prices quoted were $70/gram in New York, $85/gram in California, and $10-$20 per dosage unit in New Hampshire. The submission of Essence from the Bronx, New York contained MDMA and PCP. PharmChem Laboratories reported 20 submissions of MDMA between May, 1983 and May, 1984 when it discontinued its anonymous testing service. The MDMA samples were from Washington, California, New York, Connecticut, Massachusetts, Texas, New England and Vancouver, Canada. MDMA was submitted in capsule and powder form as MDA, MDM, MDMA, ADAM, Essence, Ecstasy, Psychedelic, and Alkaloid-based neurotransmitter.

The World Health Organization (WHO) has collected information relevant to the international scheduling of 28 phenethylamines, including MDMA. I prepared the DEA portion of the U.S. Government submission to the WHO concerning these substances and assisted in reviewing the document entitled "Critical Review of Information on 28 Uncontrolled Phenethylamines." Government document B-5) None of the countries submitting information reported that MDMA had an accepted medical therapeutic usefulness or any registered production, consumption and international trade. Canada reported that MDMA has been in Schedule H of the Food and Drugs Act since June, 1976 along with MDA, LSD and other hallucinogens. MDMA was placed under control after it appeared in the illicit drug traffic and a clandestine laboratory was found in Ontario. The Canadian government reported encounters with MDMA in 1983 and clandestine laboratories were seized in 1980 and 1983.

Information from the Federal Criminal Investigation Office (BKA) shows that there is no known legal use of MDMA in the Federal Republic of Germany, that there is no licit production of MDMA and that MDMA is not controlled under the laws of the Federal Republic of Germany. The BKA reports further indicate that local police laboratories have encountered MDMA in the illicit drug traffic. In April, 1984, capsules containing a white powder alleged to be stronger than cocaine were being sold for $20-$50 per capsule in the Baden-Wurttenburg area. Laboratory analysis determined that the substance was MDMA. Encounters with MDMA were also reported in the areas of Hessen, Rheinland-Pfalz and Hamburg.

Scientific literature published since my initial review shows that racemic MDA and MDMA have common discriminative stimulus effects in rats. (Government's Document A-6). Another publication reports that the acute lethal doses of MDA and MDMA in mice were similar; that both substances show increased lethality after aggregation, that both substances showed early signs of increased motility, followed by excitatory signs that progressed to convulsions during toxicity determinations (Government Document B-5). No literature was found describing any studies relative to the clinical utility of MDMA.

In conclusion, the information which I have collected, reviewed and evaluated along with the scientific and medical evaluation of the data by the Department of Health and Human Services show that MDMA has a high potential for abuse based on its chemical and pharmacological similarity to MDA, its self-administration without medical supervision, its clandestine synthesis and its distribution in the illicit drug traffic.

MDMA has no currently accepted medical use in treatment in the United States since there are no approved new drug applications or exemptions for MDMA as determined by the Food and Drug Administration. Accepted safety for use of MDMA under medical supervision has not been established since MDMA has no accepted medical use in treatment and has not been evaluated for safety by the Food and Drug Administration. Thus MDMA satisfies the criteria for Schedule I control under the CSA.

I declare under penalty of perjury that the foregoing statement is true and correct. Executed on April 25, 1985 at Washington, D.C.

Frank L. Sapienza

Frank L. Sapienza

UNITED STATES DEPARTMENT OF JUSTICE

DRUG ENFORCEMENT ADMINISTRATION

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

DIRECT TESTIMONY OF EDWARD CHARLES TOCUS, Ph.D.

I, Edward Charles Tocus, make the following statement:

I am a pharmacologist employed as Chief of the Drug Abuse Staff, Division of Neuropharmacological Drug Products, Center for Drugs and Biologics, United States Food and Drug Administration. I received my doctoral degree in pharmacology from the University of Chicago in 1959. From 1960 through 1966, I was employed as a Research Pharmacologist at Lederle Laboratories, Pearl River, New York. Since 1966, I have worked in the Division of Neuropharmacological Drug Products, Food and Drug Administration. I have served as a Reviewing Pharmacologist, Supervisory Pharmacologist, and Chief of the Drug Abuse Staff. A copy of my curriculum vitae is attached as Exhibit 1.

The Division of Neuropharmacological Drug Products evaluates the safety and effectiveness of new human drugs which affect the central nervous system. The Drug Abuse Staff is responsible for the evaluation of the safety and efficacy of drugs that are analgesics, narcotic antagonists,

hallucinogens, and drugs which are used to treat some form of drug dependency. The Drug Abuse Staff evaluates all drugs with an abuse liability which are submitted to the Food and Drug Administration. Evaluation normally occurs upon submission of an investigational new drug application (IND) or a new drug application (NDA). Approval of an IND allows the sponsor of a drug to legally administer that drug to humans.

The IND process is a continual monitoring and approval process which continues during the course of the studies conducted by the the sponsor. The Food and Drug Administration may stop the process at any time. The initial or original application for an IND must satisfy three elements. The first element concerns the chemistry of the drug. The sponsor must show the sources and purity of substances used in the manufacture of the drug. He must show how the drug is synthesized and that such synthesis is reproducible. The sponsor must show the composition of the drug, and must determine its purity. Any impurities must be identified and quantified. The second element involves submission of the results of animal toxicity studies. These studies are required to obtain information concerning the safety of the drug. The studies must show that the chemical in a biological system is not likely to produce irreversible damage at the doses proposed for human use. The third

element is a description of the clinical studies which will be conducted on humans. The studies must be defined in specific terms and include such things as the procedure to be followed, a definition of the population to be used, the dosages to be administered, the variables to be measured, the control observations, the statistical analyses to be used and provisions to prevent harm to the patients. The scientific qualifications of the investigators must be documented as well. The results of the human studies must be submitted to the Food and Drug Administration on an ongoing basis. The studies continue until terminated by the sponsor, stopped by FDA, or until sufficient scientific data is available for the sponsor to prepare a new drug application (NDA).

An NDA must be approved by the Food and Drug Administration prior to marketing a drug in the United States. The NDA generally consists of data which has been collected as part of the investigational new drug (IND) process. The data in the new drug application must include carcinogenic studies in animals, reproductive studies in animals, stability determinations of the product, side effects in humans, samples of labeling, 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. If the drug which is the subject

of the NDA has any chemical or pharmacologic properties which indicate that it might have an abuse liability, the NDA submission must include specific drug abuse studies.

New drug applications have been required prior to drug marketing since 1938. The statutory requirements for new drug applications and procedures regarding submission, approval, withdrawal, and revocation are found in Section 505 of the Food, Drug and Cosmetic Act. 21 U.S.C. § 355. A copy of this section is attached as Exhibit 2.

The Drug Abuse Staff of the Food and Drug Administration evaluates data included in the NDA submission, the published literature and information received from other sources such as the Drug Enforcement Administration in order to determine whether a drug has an actual and/or relative potential for abuse. After evaluation of a compound for abuse potential, the Drug Abuse Staff makes a recommendation to the Division Director, then to the Commissioner of the Food and Drug Administration (FDA) and finally with concurrence of the National Institute on Drug Abuse, to the Assistant Secretary for Health of the Department of Health and Human Services as to the propriety and necessity of scheduling such a substance under the Controlled Substances Act. As part of my duties I initiate and prepare control recommendations to be submitted to the Drug Enforcement Administration by the Assistant Secretary

for Health for drugs which have been approved in the NDA process. There are occassions when drugs which have not been evaluated by the Drug Abuse Staff as part of the NDA process come to the attention of the staff. This occurs primarily when the Drug Enforcement Administration submits a control recommendation to the Assistant Secretary for Health for a scientific and medical evaluation and recommendation as required by the Controlled Substances Act. As part of my duties I evaluate control recommendations submitted to the Assistant Secretary for Health by the Drug Enforcement Administration and prepare the control recommendations which will be sent to the Administrator of DEA by the Assistant Secretary for Health.

In March, 1984 the then-Administrator of the Drug Enforcement Administration sent a letter and a document entitled, "Schedule I Control Recommendation Under the CSA for 3,4-Methylenedioxymethamphetamine (MDMA)" to the Assistant Secretary for Health. The DEA Administrator asked for a scientific and medical evaluation and a scheduling recommendation for MDMA in accordance with 21 U.S.C. § 811(b). The control document sent by DEA contained information concerning the abuse potential, references from the scientific literature and statistics on the illicit trafficking of MDMA which had been collected by DEA staff. The March 13, 1984 letter to the Assistant

Secretary for Health and the control document were forwarded to me for evaluation. Prior to the receipt of information from the Drug Enforcement Administration, I had had no specific knowledge or information concerning the drug MDMA. I reviewed the data contained in the DEA document, and searched the files of the Food and Drug Administration for information concerning the drug 3,4-methylenedioxymethamphetamine (MDMA). I found no reference in the files of the Food and Drug Abministration to this drug. 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. Based on the review of the files of the Food and Drug Administration, I was able to conclude that the substance or drug 3,4-methylenedioxymethamphetamine had not been approved for human research studies, or for marketing in the United States. I then applied the eight factor analysis required by the Controlled Substances Act using the data which had been submitted by the Drug Enforcement Administration in their control document. My conclusions based upon the application of the data supplied by DEA to the eight factor analysis are as follows:

1. The actual or relative potential for abuse of MDMA is evidenced by its chemical and pharmacological similarity

to the Schedule I controlled substance MDA. Actual abuse of MDMA has been shown by submissions of MDMA to DEA laboratories, seizures of MDMA, evidence of clandestine manufacture of MDMA, and mentions of MDMA in the Drug Abuse Warning Network. MDMA has been identified in 34 submissions to DEA laboratories from 12 states in an 11 year period. Clandestine laboratory seizures involving the manufacture of MDMA have been identified in four states. MDMA has received 8 Drug Abuse Warning Network (DAWN) mentions and one medical examiner report since 1972. These mentions indicate the existence of human use of MDMA.

2. Scientific studies have shown that the pharmacological effect of MDMA is similiar to that of MDA. MDMA and MDA both have analgesic activity in several procedures in mice, and both substances have been shown to produce increased motor activity or stimulant activity in mice. When tested in dogs and monkeys MDMA produced a spectrum of central nervous system, autonomic nervous system and motor activity similar to that obtained with MDA and mescaline, also a Schedule I controlled substance. Tests in humans have shown MDMA to be similar to MDA. Both substances produced a change in consciousness without hallucination, a decrease in tension, a heightening of mood, and an increase in acoustic, visual and tactile perception. Both MDMA and MDA cause increased heart rate and mydriasis.

3. The current scientific knowledge concerning MDMA is that it is chemically and pharmacologically related to the substance 3,4-methylenedioxyamphetamine (MDA) which is currently a Schedule I controlled substance under the Controlled Substances Act. This relationship is the same that amphetamine bears with methamphetamine, both Schedule II controlled substances, which is that there is a methyl group on the nitrogen of the amine. This difference is reflected in the chemical names of the substances - methamphetamine and 3,4-methylenedioxymethamphetamine, which contain "meth" for the methyl group. MDMA can be synthesized easily using readily available materials. Several alternative pathways for the synthesis of MDMA have been described in the scientific literature. Several synthetic methods of making MDMA have also been identified through the chemicals seized in clandestine laboratories.

4. The history and current pattern of abuse of MDMA was shown by DEA in its document describing laboratory submissions, seizures, clandestine laboratory operations, and DAWN mentions.

5. The scope, duration, and significance of abuse were shown in the DEA document by describing evidence of consistent illicit trafficking since 1970.

6. MDMA can produce harm to the public health. Studies in experimental animals which were included in the

DEA document indicate that MDMA is more toxic than mescaline and less toxic than MDA on a milligram basis.

7. There was no specific data available concerning the psychic or physiological dependence liability of MDMA.

8. MDMA is not an immediate precursor of a substance already controlled under the Controlled Substances Act.

After reviewing the eight factor analysis I concluded that MDMA satisfies the three criteria for Schedule I control. MDMA has a high potential for abuse. This is evidenced by its pharmacological similarity to the Schedule I substance MDA and evidence of its actual abuse. MDMA has no currently accepted medical use in treatment in the United States. This is because MDMA has not been approved by the FDA for marketing in this country. It is not a grandfathered drug, it does not have an approved NDA, and it has not been approved for over-the-counter use. MDMA lacks accepted safety for use under medical supervision. A substance cannot be deemed safe unless FDA has determined that there is scientific data which demonstrates that a substance can be given to humans without irreversible harm. No scientific data has been supplied to FDA which would demonstrate the safety of the drug, MDMA. A review of the available scientific literature on MDMA does not support the safety of the drug for use under medical supervision. If the safety of a drug cannot be established, then the drug lacks accepted safety.

After review and evaluation of the DEA document in conjunction with the eight factor analysis, finding that MDMA has not been approved by the Food and Drug Administration for marketing in the United States, and in the interest of preventing actual and significant harm to the public health, I concluded that MDMA should be controlled in Schedule I of the Controlled Substances Act.

I declare under penalty of perjury that the foregoing statement is true and correct.

Executed on April 22, 1985.

Edward Charles Tocus

Edward Charles Tocus, Ph.D.

EXHIBIT 2

TITLE 21—FOOD AND DRUGS

Section 505
Food, Drug and Cosmetic Act

§ 355. New drugs

(a) Necessity of effective approval of application

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.

(b) Filing application; contents

Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (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.

(c) Period for approval of application; period for, notice, and expedition of hearing; period for issuance of order

Within one hundred and eighty days after the filing of an application under this subsection, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(1) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) of this section applies, or

(2) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) of this section on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(d) Grounds for refusing application; approval of application; "substantial evidence" defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not 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; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

(e) Withdrawal of approval; grounds; immediate suspension upon finding imminent hazard to public health

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary

finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) that the application contains any untrue statement of a material fact: *Provided*, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (j) of this section or to comply with the notice requirements of section 360(j)(2) of this title, or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based.

(f) Revocation of order refusing, withdrawing or suspending approval of application

Whenever the Secretary finds that the facts so require, he shall revoke any previous order under subsection (d) or (e) of this section refusing, withdrawing, or suspending approval of an application and shall approve such application or reinstate such approval, as may be appropriate.

(g) Service of orders

Orders of the Secretary issued under this section shall be served (1) in person by any officer or employee of the Department designated by the Secretary or (2) by mailing the order by registered mail or by certified mail addressed to the applicant or respondent at his last-known address in the records of the Secretary.

(h) Appeal from order

An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals or the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of title 28. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28. The commencement of proceedings under

this subsection shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

(i) Exemptions of drugs for research; discretionary and mandatory conditions; direct reports to Secretary

The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of the public health, provide for conditioning such exemption upon—

(1) the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, of preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing;

(2) the manufacturer or the sponsor of the investigation of a new drug proposed to be distributed to investigators for clinical testing obtaining a signed agreement from each of such investigators that patients to whom the drug is administered will be under his personal supervision, or under the supervision of investigators responsible to him, and that he will not supply such drug to any other investigator, or to clinics, for administration to human beings; and

(3) the establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application pursuant to subsection (b) of this section.

Such regulations shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational purposes certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any control used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where they deem it not feasible or, in their professional judgment, contrary to the best interests of such human beings. Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs.

(j) Records and reports; required information; regulations and orders; access to records

(1) In the case of any drug for which an approval of an application filed pursuant to subsection (b) of this section is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) of this section: *Provided, however,* That regulations and orders issued under this subsection and under subsection (i) of this section shall have due regard for the professional ethics of the medical profession and the interests of patients and shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulations or orders are applicable, of similar information received or otherwise obtained by the Secretary.

(2) Every person required under this section to maintain records, and every person in charge or custody thereof, shall upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

(June 25, 1938, ch. 675, § 505, 52 Stat. 1052; 1940 Reorg. Plan No. IV, § 12, eff. June 30, 1940, 5 F.R. 2422, 54 Stat. 1237; 1953 Reorg. Plan No. 1, § 5, eff. Apr. 11, 1953, 18 F.R. 2053, 67 Stat. 631; June 11, 1960, Pub. L. 86-507, § 1(18), 74 Stat. 201; Oct. 10, 1962, Pub. L. 87-781, title I, §§ 102(b)–(d), 103(a), (b), 104(a)–(d)(2), 76 Stat. 781-783, 784, 785; Aug. 16, 1972, Pub. L. 92-387, § 4(d), 86 Stat. 562.)

UNITED STATES DEPARTMENT OF JUSTICE

DRUG ENFORCEMENT ADMINISTRATION

In the Matter of)
)
MDMA SCHEDULING)

DIRECT TESTIMONY OF LEWIS S. SEIDEN, Ph.D.

1. I, Lewis S. Seiden, make the following statement:

I am a Professor in the Department of Pharmacological and Physiological Sciences at the University of Chicago and I hold joint appointments in the Department of Psychiatry and the College. I have been a faculty member at the University of Chicago since 1965. I received B.A. and B.S. degrees from the University of Chicago in 1956 and 1958, respectively and a Ph.D. in 1962 from the same Institution. I was a Postdoctoral Fellow in the Department of Pharmacology at the University of Goteborg in Sweden from 1962 to 1963 and I was a Postdoctoral Fellow at Stanford University, Department of Pharmacology from 1964 until 1965. I have been engaged as a research scientist in the fields of psychopharmacology and neuropharmacology and a copy of my curriculum vitae is attached as exhibit 1.

2. 3,4-Methylenedioxymethylamphetamine (MDMA) may be toxic to serotonin (5-hydroxytryptamine, 5HT) neurons in the human brain. If so, this would be serious because the 5HT cells are believed to play a major role in pain perception, sleep, and affect the regulation and expression of aggressive and sexual behavior.

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3. In my laboratory, we have not examined MDMA effects in humans or lower animals, but based on work in 3 other species with closely related compounds, I believe that there is sufficient evidence to proceed with great caution in using this drug. The evidence which supports this conclusion is outlined below

a) First, methylamphetamine (MA, a structurally related compound; see exhibits 2 and 3), has long lasting effects on both dopamine (DA), and 5HT neurons in the central nervous system when administered in relatively high but short duration, or repeated but lower doses (exhibit 4). Following several dosing regimes, there is a decrease in steady state levels of DA and 5HT in various brain regions for weeks after discontinuation of the drug in rats (exhibit 7). DA is depleted in the striatum, the limbic system and the frontal cortex for as long as 8 weeks after the administration of MA and there is no sign of recovery. The depletion of 5HT does not seem to last as long as DA; in fact at 8 weeks, levels in some brain regions returned to near normal. However, the question remains open whether the apparent sprouting of 5HT neurons restores functionally normal synapses. And in addition to the depletion of DA and 5HT, we and others have observed a decrease in the enzymes which control the rate of synthesis of these transmitters, and a decrease in the number of their uptake sites. <u>In vitro</u> measurement of

kinetic constants revealed a decrease in the number of enzyme molecules and a decrease in the number of uptake sites; the affinity constants for both synthesis and uptake did not change. These results are consistent with nerve terminal degeneration. Finally, we have obtained direct anatomical evidence of nerve terminal degeneration using the Fink-Heimer staining procedures (exhibit 8).

b. Second, amphetamine (exhibit 9) causes patterns of neurochemical change very similar to those just described for methylamphetamine (although there are slight differences in the dose required).

c. Third, with both methylamphetamine and amphetamine, we have obtained evidence suggesting degeneration of neurons in rats, guinea pigs and rhesus monkeys (exhibit 4). Other investigators have obtained similar evidence in mice and cats. Given the consistent results among five diverse mammalian species, one would logically infer that the same damage could occur in humans.

d. Fourth, we find methylendixoyamphetamine (MDA) is toxic to 5HT fibers in rats (exhibit 10), using both chemical and anatomical criteria. MDA has these effects at much lower doses than those required to achieve the same effects with amphetamine or methylamphetamine.

e. MDA is chemically related to amphetamine, the major

difference being the presence of the dioxymethylene group at the 3 and 4 position of the phenyl ring. The major difference between MDMA and MDA is the presence of a methyl group on the terminal nitrogen. In our experimental work, the methyl group (i.e., MA) on amphetamine (A) did not confer any less neurotoxicity on this molecule (see above).

4. Therefore, I strongly suspect that MDMA will have a profile of neurotoxicity similar to that of MDA. It is true that we have not yet tested MDA in species other than rats, but again we have found that all compounds of this group so far tested show species generality. Based on the evidence available I would predict that MDA and MDMA will have the same neurotoxic effects in other mammalian species, including humans. Close chemical analogs of MDMA including MA, A, and MDA are toxic in brain, and this makes it appear extremely likely that MDMA will produce similar toxic effects. Further, as shown with MDA, the drug is toxic in the rat at doses that are very low when compared to toxic doses of MA or A. This is true regardless of whether dose is measured on a molar or an efficacy basis. This would suggest that humans taking MDA or MDMA in doses such as 100-120 mg could undergo similar toxic effects.

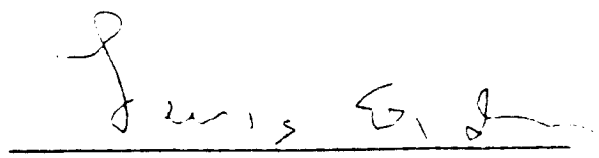
5. MDMA has a neurotoxic potential in humans yet to the best of my knowledge, this compound has not been systematically screened for efficacy for the treatment of mood or behavioral disorders. The evidence attesting to its efficacy

as presented for example by Dr. Richard Ingrasci, is not controlled by double blind procedures comparing placebo to MDMA. The claim that MDMA has beneficial effects is suspect because of the multiplicity of variables that are confounded with taking the drug: e.g., fasting for 4-6 hrs, couples taking the drug together, being encouraged by the therapist to talk to significant others in an intimate setting, and writing down the results of the entire experience. In addition, Dr. Ingrasci regrettably presents no systematic summary of the cases he has observed but rather presents a few anecdotal cases. These few anecdotal cases, so mixed with other treatment variables hardly make a case for the specific efficacy of this compound.

6. In a drug trial the preliminary case for efficacy must be weighed against the potential for harmful side effects. The case to date that MDMA is an effective drug seems weak; furthermore, there is evidence to suggest that the drug could harm 5HT cells in brain. As noted above, 5HT cells are believed to play a major role in pain perception, sleep, and to affect regulation and expression of aggressive and sexual behavior. It would follow from the above evidence that clinical scientists should conduct trials of MDMA in humans only with the utmost caution. They should ensure that the potential benefits to the person is great enough to outweigh the risks, and they should collect the data in a systematic and well controlled manner as is usually done under an Investigational New Drug Permit.

I declare under penalty of perjury that the foregoing statement is true and correct.

Executed on May 15, 1985



Lewis S. Seiden, Ph.D.

UNITED STATES DEPARTMENT OF JUSTICE

DRUG ENFORCEMENT ADMINISTRATION

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

REBUTTAL TESTIMONY OF LARRY SNYDER

I, Larry Snyder make the following statement: I am a Supervisory Diversion Investigator with the Drug Enforcement Administration. I have been an Investigator with DEA for 14 years. Prior to this I was employed by Rexall Drug Company in St. Louis, Missouri as Manager of Quality Control, and by the Food and Drug Administration for three years. I was an Inspector with FDA and conducted investigations relating to New Drug Applications (NDAs) and Investigational New Drug Applications (INDs). I am currently assigned to the Office of Diversion Control as Unit Chief of Domestic Operations in the Diversion Operations Section in DEA Headquarters in Washington, D.C. During the time I have been with DEA I have served as an Investigator in DEA's St. Louis, Missouri office, a Supervisor and Program Manager in DEA's Kansas City office, and a Program Manager for the Chicago Division in DEA's Chicago Divisional Office. During the course of my duties as an Investigator and a Supervisor, I have had the opportunity to conduct and supervise investigations of DEA registrants, including Schedule I researchers. I am familiar with the registration, security and recordkeeping requirements imposed by the Controlled Substances

Act and implementing regulations.

An individual who is registered by DEA to conduct research with controlled substances in Schedule I is required to maintain records in order to account for these controlled substances. A researcher must physically inventory the stock of controlled substances on hand every two years. Records of receipt for all controlled substances must be maintained. Controlled substances in Schedules I and II require the receipts to be in the form of a triplicate order form issued by DEA. This form is used to order Schedule I and II controlled substances from the supplier and the third copy is retained by the purchaser (researcher). Upon receipt of the controlled substance a notation of the quantity and date received is made on the third copy and retained by the researcher as the record of receipt. The researcher must also document all dispostions of controlled substances such as administering, dispensing, waste, theft, or transfer to another researcher. These records may be maintained in any format which is convenient for the researcher, as long as they contain the required information. All records must be maintained separately and for a period of two years.

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 substances is required; records of receipt, but not on DEA triplicate order forms, and complete and accurate records of disposition in the same manner as Schedule I

and II researchers.

In addition, there is an exemption from the recordkeeping requirements for individuals who conduct research under the authority and auspices of a New Drug Application (NDA) or an Investigational New Drug Application (IND) or conduct preclinical research in an institutional setting. Where the insitution keeps records of the controlled substances, the individual researcher is exempt from such requirements. Based upon my previous experience, the records required to be kept in accordance with IND and NDA procedures are significantly more onerous than those required by DEA. The records required to be kept in the course of scientific experimentation are far more detailed than those required to account for the controlled substances used by researchers.

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.

I declare, under penalty of perjury, that the foregoing statement is true and correct.

Larry Snyder

Dated: May 16, 1985

000153

Exhibit 10

Hallucinogenic Amphetamine Selectively Destroys Brain Serotonin Nerve Terminals: Neurochemical and Anatomical Evidence

Abstract. (±)-3-4-Methylenedioxyamphetamine (MDA), an amphetamine analogue with hallucinogenic activity, produced selective long-lasting reductions in the level of rat brain serotonin (5HT), the number of 5HT uptake sites and the concentration of 5-hydroxyindoleacetic acid (5HIAA). Morphological studies suggested that these neurochemical deficits were due to 5HT nerve terminal degeneration. These results show that MDA possesses brain 5HT neurotoxic activity and raise the question of whether exposure to MDA and related hallucinogenic amphetamines can produce brain 5HT neurotoxicity in humans.

Keywords: Neurotoxicity - Serotonin - Amphetamines - Hallucinogenic Drugs

(+)-3,4-Methylenedioxyamphetamine (MDA) is a synthetic amphetamine derivative which produces a mixture of psychomotor stimulant and hallucinogenic effects (1). This combination of psychotropic actions may stem from MDA's close structural relationship to both amphetamine, a prototypic stimulant, and mescaline, a well-known hallucinogen. Clinically, MDA has been evaluated as an anorectic, antidepressant and as an adjunct to psychotherapy (2). Although some investigators have advocated that MDA be used to facilitate psychotherapy, MDA has yet to find an accepted place in the medical pharmacopoeia. In contrast, MDA has been a popular illicit drug for over 20 years (3). Despite recognition of MDA's high abuse liability, relatively little research has been done to assess its toxicity. The few studies performed in animals indicate that the toxicity of MDA generally parallels that of amphetamine (4). As such, MDA can produce mydriasis, profuse salivation, tachycardia, hypertension, hyperthermia, convulsions and death. The few studies done in humans suggest that in doses up to 300 mg MDA is free of significant toxicity (2). Higher MDA doses have been associated with near fatal as well as fatal reactions (5). Marked physical exhaustion lasting up to 48 hours after drug ingestion (100-300 mg) has been reported (6).

Amphetamines such as d-methamphetamine and d-amphetamine are toxic to brain dopamine (DA) and serotonin (5HT) neurons (7). This toxicity is manifested by long-lasting reduction in the levels of DA and 5HT and a decreased number of uptake sites in the brain (7). In the case of DA neurons, these deficits have been shown to be the result of DA nerve terminal degeneration (8). In light of these findings and in view of the paucity of information on MDA toxicity, the present study evaluated the DA, 5HT and norepinephrine (NE) neurotoxic potential of MDA. We now present chemical and anatomical evidence of selective brain 5HT nerve terminal degeneration after single or multiple doses of MDA.

We examined the neurotoxic potential of various doses (1.25, 2.5, 5, 10, 20 and 40 mg/kg) of MDA by administering each of these doses subcutaneously to a group

(+)-3,4-Methylenedioxyamphetamine (MDA) is a synthetic amphetamine derivative which produces a mixture of psychomotor stimulant and hallucinogenic effects (1). This combination of psychotropic actions may stem from MDA's close structural relationship to both amphetamine, a prototypic stimulant, and mescaline, a well-known hallucinogen. Clinically, MDA has been evaluated as an anorectic, antidepressant and as an adjunct to psychotherapy (2). Although some investigators have advocated that MDA be used to facilitate psychotherapy, MDA has yet to find an accepted place in the medical pharmacopoeia. In contrast, MDA has been a popular illicit drug for over 20 years (3). Despite recognition of MDA's high abuse liability, relatively little research has been done to assess its toxicity. The few studies performed in animals indicate that the toxicity of MDA generally parallels that of amphetamine (4). As such, MDA can produce mydriasis, profuse salivation, tachycardia, hypertension, hyperthermia, convulsions and death. The few studies done in humans suggest that in doses up to 300 mg MDA is free of significant toxicity (2). Higher MDA doses have been associated with near fatal as well as fatal reactions (5). Marked physical exhaustion lasting up to 48 hours after drug ingestion (100-300 mg) has been reported (6).

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We examined the neurotoxic potential of various doses (1.25, 2.5, 5, 10, 20 and 40 mg/kg) of MDA by administering each of these doses subcutaneously to a group

(N=4) of rats every twelve hours for four consecutive days and then assessing the effect of these MDA dosing regimens on brain DA, 5HT and norepinephrine (NE) levels measured two weeks after drug treatment (9). Doses were selected to cover a range known to produce from minimal to maximal behavioral effects in rodents (4,10). Regional brain DA, 5HT and NE level determinations two weeks after drug treatment revealed that MDA produced a large depletion of 5HT in various brain regions without affecting the level of either DA or NE in these same regions (Table 1). The lowest dose of MDA in producing this change was 5 mg/kg. This MDA regimen lowered 5HT levels in the hippocampus and rest of brain but not in the striatum (Table 1). Higher dose regimens reduced 5HT levels in all of the brain regions examined. Of note is that even the highest dose (40 mg/kg) regimen of MDA produced no lethality and that two weeks after drug administration MDA treated rats could not be distinguished from control rats by casual observation.

We examined two other 5HT neuronal markers following MDA administration. Rats were administered 10 mg/kg of MDA for 4 days and two weeks later they were killed for hippocampal ^{3}H-5HT uptake and 5-hydroxyindoleacetic acid (5HIAA) level measurements. Kinetic analysis of ^{3}H-5HT uptake (11) by crude synaptosomal suspensions prepared from the hippocampus of saline- and MDA-treated rats indicated that MDA produced a long-lasting reduction in the V_{max} of ^{3}H-5HT uptake without affecting its K_m (V_{max} in controls: 7479 $\pm$ 678 cpm; in MDA rats: 3265 $\pm$ 408 cpm, difference significant at 0.01 level; K_m in controls 0.12 $\pm$ 0.03 uM; in MDA rats 0.16 $\pm$ 0.04 uM, non-significant difference). This result indicates that MDA reduces the number but not the affinity of synaptosomal 5HT uptake sites. 5HIAA level determinations (12) indicated that MDA also produced a long-lasting reduction in 5HIAA concentration in the hippocampus (5HIAA in control rats: 0.33 $\pm$ 0.03 ug/g; in MDA rats: 0.12 $\pm$ 0.01 ug/g, difference significant at 0.01 level). This finding, along with the observations of

decreased 5HT level and uptake following MDA administration, strongly suggest that MDA is toxic to 5HT neurons.

To confirm this, we looked for evidence of 5HT nerve terminal destruction following MDA administration using the Fink-Heimer method (13) which allows for selective silver-impregnation of degenerating axons and terminals. With this method, degenerating nerve terminals were found in the hippocampus and striatum of all three rats administered MDA (Figure 1). No such terminal degeneration was found in any of the three control rats. Given that the hippocampus and striatum are the same brain regions in which MDA produced selective long-lasting 5HT depletions (Table 1), it seems reasonable to conclude that the degenerating nerve terminals in Figure 1 are serotonergic and that the way in which MDA induces prolonged 5HT neurochemical deficits is by destroying 5HT nerve terminals.

In a final experiment rats were administered 10 mg/kg of MDA every twelve hours for 4, 2, 1 and 0.5 days and killed two weeks later. 5HT level determinations at this time revealed that a single 10 mg/kg injection of MDA (0.5 day regimen) reduced hippocampal 5HT content by 32% and that additional injections led to greater 5HT deficits (Table 2).

Our study raises the question of whether MDA produces 5HT neurotoxicity in humans. Given differences in species, dose, frequency and route of administration, as well as differences in the way in which rats and humans metabolize amphetamine (14), it would be premature to extrapolate our findings to humans. It should also be noted that the doses of MDA required to produce 5HT neurotoxicity in the rat (5-10 mg/kg, Tables 1 and 2) are roughly three to five times higher than those required to produce hallucinogenic effects (approximately 1.5 to 3 mg/kg (1,2). Hence, doses of MDA generally ingested by humans may not be sufficiently high to induce 5HT neurotoxicity, unless humans prove to be more sensitive than rats to the toxic effects of MDA. That this may be the case is suggested by the observation that a 7.5 mg/kg dose of MDA

approaches the lethal dose in humans (5) whereas in rats even a 40 mg/kg regimen did does not produce any lethality.(vida supra).

Other ring-substituted amphetamines such as 3,4-methylenedioxymethamphetamine (MDMA), 3,4,5-trimethoxyamphetamine (TMA) and 2,5-dimethoxy-4-methylamphetamine (DOM) are widely abused and possible toxic effects on 5HT neurons of these ring substituted amphetamines need to be evaluated. Such studies should help identify the structural requirements for a ring-substituted amphetamine to produce 5HT neurotoxicity. A better understanding of such structure-activity relations could be of value in suggesting ways in which endogenous substances (e.g. biogenic amines and free phenylethylamines) which are structurally related to MDA and other toxic amphetamines might be modified in vivo into neurotoxic compounds. Such endogenously formed neurotoxins (15) could play a role in the etiology of neurodegenerative disorders involving monoamine-containing neurons in the central nervous system of humans.

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9. Male albino Sprague-Dawley rats weighing approximately 250 grams were obtained from the Holtzman Co. (Madison, WI) and housed singly in suspended wire-mesh cages with free access to food (Purina Rat Chow) and water in a colony room maintained at 23±1 C. (±)-MDA hydrochloride was obtained from the National Institute on Drug Abuse. Its purity was confirmed by means of mass spectroscopic analysis. MDA was administered subcutaneously after being dissolved in sterile 0.9% saline at various desired concentrations. Dose (expressed as the free base) was adjusted by injecting each of these MDA solutions on a 1 ml/kg basis. Control rats were injected with an equal volume of saline. Regional brain DA, 5HT and NE levels were determined by high performance liquid chromatography coupled with electrochemical detection. DA and 5HT were measured according to the method of R. Keller, A. Oke, I. Mefford, R. Adams, Life Sciences 19, 995 (1976), as modified in this laboratory (J. Lucot, J. Horwitz, L.S. Seiden, J. Pharmacol. Exp. Ther. 217, 738 (1981). NE was analyzed using the method of R.S. Fenn, S. Siggia, D.J. Curran, Analyt. Chem. 50 (8), 1067 (1978).

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11. ^{3}H-5HT uptake by crude synaptosomal hippocampal suspensions was measured and kinetically analyzed as described previously; G.A. Ricaurte, L.S. Seiden, C.R. Schuster, Brain Res. 193, 153 (1980). The only important difference was that hippocampal tissue was homogenized in 25 rather than 50 volumes (w/v) of 0.32 M sucrose.

12. 5HIAA levels were measured using reverse-phase high performance liquid chromatographic procedures as outlined by C. Kotake, G. Vosmer, T. Heffner and L. Seiden. Pharmacol. Biochem. Behav. 22, 85 (1985).

13. Prior to doing terminal degeneration studies in MDA treated rats the ability of the Fink-Heimer method to demonstrate 5HT terminal degeneration was assessed. 75 micrograms of 5,7,DHT were dissolved in 0.9% NaCl containing ascorbic acid and injected into the left lateral ventricle. 18 hours later terminal degeneration was found in both the rat hippocampus and striatum. This short survival time seems critical as terminal degeneration is not observed after longer survival times. R.P. Fink and L. Heimer, Brain Res. 4, 369 (1967); V.J. Massari, Y. Tizabi, E. Sanders-Bush, Neuropharmacology 17, 54 (1978).

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16. We gratefully ackowledge the skillful assistance of Pat Cantwell in the preparation of the manuscript. G.A. Ricaurte was supported by USPHS GM-07109. This research was supported by grants from NIDA: DA-00085 and DA-00250 (C.R. Schuster, P.I.). L.S. Seiden is the recipient of RSA MH-10562; C.R. Schuster is also a recipient of an RSA DA-00024.

Table 1

Regional Brain Monoamines Two Weeks After Various Doses of MDA[1]

	Striatum		Hippocampus		Rest of Brain		
	DA[2]	5HT	NE	5HT	DA	NE	5HT
Treatment							
Saline	11.6±0.3	0.43±-0.05	0.34±0.02	0.41±0.02	0.19±0.01	0.46±.01	0.32±0.04
MDA							
1.25 mg/kg	10.6±0.4	0.42±0.02	NM[3]	0.39±0.03	0.17±0.01	NM	0.29±0.01
2.5 mg/kg	11.7±0.4	0.37±0.04	NM	0.40±0.02	0.18±0.01	NM	0.34±0.03
5 mg/kg	12.4±0.7	0.36±0.04	NM	0.28±0.04*	0.18±0.01	NM	0.23±0.03*
10 mg/kg	11.5±0.6	0.18±0.05*	0.31±0.06	0.16±0.05*	0.18±0.02	0.46±0.04	0.19±0.02*
20 mg/kg	10.6±0.4	0.14±0.02*	0.38±0.01	0.10±0.01*	0.17±0.02	0.47±0.01	0.16±0.02*
40 mg/kg	10.8±0.5	0.11±0.01*	0.40±0.02	0.10±0.01	0.18±0.02	0.43±0.02	0.15±0.02*

[1]Each MDA dose was administered approximately every 12 hours for 4 consecutive days.

[2]Values represent the mean ± S.E.M. expressed in ug/g tissue (N=4).

[3]Not measured since these MDA doses produced little or no effect on 5HT.

*$p < 0.05$, two-tailed student's t-test.

Table 2

Hippocampal 5HT Content Two Weeks After
Various 10 mg/kg Regimens of MDA

Regimen Duration	Hippocampal 5HT	% Decrease
Control	0.41 ± 0.02	-
0.5 day	0.28 ± 0.04*	32
1 day	0.17 ± 0.01*	59
2 days	0.12 ± 0.01*	74
4 days	0.10 ± 0.01*	76

* Significantly different from saline control ($p < 0.05$).

Fig. 1 Legend. Coronal silver-stained sections through the striatum of (A) control rat and (B) a rat administered 10 mg/kg of MDA subcutaneously twice, 12 hours apart. Fink-Heimer method (Procedure I) with cresyl-violet counter-stain. 18 hour survival.

Tr. 3, July 10, 1985 - Dkt. No. _____

EXCERPT

SEIDEN - 60-62

Tr. 3

UNITED STATES DEPARTMENT OF JUSTICE

Drug Enforcement Administration

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

Room 225,
United States Courthouse,
811 Grand Avenue,
Kansas City, Missouri,

Wednesday, July 10, 1985.

The above-entitled matter came on for hearing, pursuant to notice, at 10:13 o'clock a.m.

BEFORE:

HON. FRANCIS L. YOUNG, Administrative Law Judge.

APPEARANCES:

STEPHEN E. STONE, Esq., and CHARLOTTE A. JOHNSON, Esq., Office of Chief Counsel, Drug Enforcement Administration, 1405 I Street, Northwest, Washington, D.C. 20537, appearing for the Drug Enforcement Administration.

RICHARD COTTON, Esq., Davey, Ballantine, Bushby, Palmer & Wood, 1775 Pennsylvania Avenue, Northwest, Washington, D.C. 20006, appearing for Drs. Greer and Grinspoon, Professors Bakalar and Roberts.

LYN B. EHRNSTEIN, Esq., was not present.

ALSO PRESENT:

MELANIE L. BALTZ, Hearing Clerk.

-dg-18

these three more important, or less important, than any of the others?

A It would depend upon the function one was talking about.

If one is talking about motor functions, for example, dopamine is a very important transmitter.

If one is talking about sleep, serotonin seems to be more important.

So you can't say that they are more important. You have to relate the function you are talking about, to the importance of the transmitter compound. They are all important to the brain.

Q Before we turn to the papers that are here, it is my understanding from statements that the government counsel have made that you were going to undertake an experiment with MDMA along the lines of the experiment included with your testimony on MDA. Have you undertaken such an experiment?

A Yes, we have.

Q What is the current status of that experiment?

A We are about halfway through the chemical analyses.

We have done some very preliminary histopathological analyses; and that is where we stand.

We have some results.

3 dg-19

Q And what are those results that you have currently?

A Just to summarize them briefly, we have looked at serotonin levels and dopamine levels in two areas of the brain so far. In rats, that have been treated with differing doses of MDMA for four days, they would receive the drug twice a day by subcutaneous injection.

Let me refer to my notes here.

We used a total of twenty, forty, and eighty milligrams per kilogram, per day, for a period of four days.

Then we would discontinue the doses for a period of two weeks, in which the animals received no drugs at all. And, at that point, the animals were sacrificed and their brains were removed and appropriately dissected into various regions.

What we found out--let me see. We have analyzed two regions so far. The hippocampus and the cerebral cortex, both of which contained significant amounts of serotonin, or 5-HT, and we find that we find depletions of 5-HT at all the doses that we tested.

For the lowest dose, the depletion in the cortex--the lowest dose being 20 milligrams per day--was 50 per cent.

And for the highest dose, it was over 90 per cent. That was in the cortex.

And, essentially, the same results were true of

3 dg-20

We are currently doing testing with single injections and we are testing different regions of the brain, but those results are still not in, as of yet, and my understanding is that they will be introduced when we have completed the work.

Q When you mention the single-injection tests, are those the same type of tests that you performed with MDA?

A Yes; exactly.

Q Could you just describe the procedure that you used with those single-injection tests, with respect to MDMA?

A With respect to MDA or MDMA?

Q MDMA.

A They are exactly the same as these, except instead of giving the animal two injections for a period of four days, we just give it one injection and then wait two weeks.

Q You wait two weeks and then you sacrifice the animal?

A That's right, and then we look at the brain chemistry.

Q In looking at the brain chemistry, you use the stain that you referred to in your paper as the Fink-Heimer Stain?

A No. No. The brain chemistry is done two weeks later. The signs of neuronal degeneration occur much

Tr. 5, October 8, 1985 - Dkt. No. 126

EXCERPTS

SAPIENZA CROSS -	61-63 90-92
ZINBERG REDIRECT -	172-176

Tr. 5

UNITED STATES DEPARTMENT OF JUSTICE

DRUG ENFORCEMENT ADMINISTRATION

- - - - - - - - - - - - - - - - X

In the Matter of: :

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MDMA SCHEDULING : Docket No. 84-48

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Tuesday,
October 8, 1985

U.S. Claims Court
717 Madison Place, N.W.
Room 309, Courtroom 10
Washington, D. C.

The above entitled matter came on for hearing, pursuant to notice, at 10:12 a.m.

BEFORE: FRANCIS L. YOUNG
Administrative Law Judge

APPEARANCES:

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APPEARANCES: (Continued)

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ALSO PRESENT:

MELANIE L. BALTZ, Hearing Clerk

I N D E X

WITNESSES:	DIRECT	CROSS	REDIRECT	RECROSS
Frank L. Sapienza	--	33	105	
Richard Yensen, PhD	--	114	137	
Dr. Norman E. Zinberg	--	152	172	
Dr. Lance S. Wright	--	141	150	
Dr. Joel E. Kleinman	--	179	206	

E X H I B I T S

	Identified:	Received:
Government B-20	--	6
Agency's 41-47	--	7
Sapienza's Cross Examination Exhibit 1	45	45

A. I don't have that information handy.

Q. When you compiled Attachment 1, did you make that inquiry of the STRIDE computer people?

A. No, I did not.

Q. And you didn't include that evidence or that information in this attachment or this document that went to the Department of Health and Human Services, is that correct?

A. That wasn't relevant to this either. We're looking at MDMA, not MDA.

Q. And so you wouldn't contend that there's any relevance with respect to any information with respect to MDA in connection with the scheduling of MDMA, is that your testimony

A. No, it is not. In connection with the STRIDE exhibits from DEA laboratories, there is very little connection, except that some of the exhibits of MDMA came in as MDA. MDA, if I may explain --

JUDGE YOUNG: Yes.

BY MR. COTTON:

Q. Absolutely.

A. MDA is and has been a Schedule 1 controlled substance. As such, it is the subject of many investigations in our Agency, since it's a Schedule 1 substance.

MDMA is not controlled, or has not been controlled until July 1st, with the emergency scheduling. The number of exhibits of non-controlled substances which come into our

laboratories from investigations specifically aimed at those substances, is usually very very small. And to compare the number of exhibits of a substance which is a new drug of abuse and is not controlled versus one which has been in Schedule 1 for many years, is rather meaningless.

As an example, since July 1st, since MDMA has been controlled in Schedule 1, our laboratories have anlayzed 14 exhibits of MDMA containing 35,000 dosage units, from Texas alone. So comparing a Schedule 1 drug with another Schedule 1 drug in the amount of analyses, may have some merit. Comparing the Schedule 1 drug with a non-controlled drug, has very little merit.

Another example, these so-called designer drugs, the phentonylanalogs for example, which are occurring on the West Coast, our laboratories are encountering one, two or three of those per year, but yet they are causing significant numbers of death and so forth in California and the number of those encounters do not compare in any with the number of heroin deaths that we get.

But yet those one, two or three encounters are very significant.

Q In terms of any other drugs that were not controlled during this period, what inquiries did you make in terms of the STRIDE systems containing those substances?

A For this report, I didn't make any. We don't try

to compare substances, one with the other. STRIDE is not a quantitative estimate of the amount of the material that's on the street.

It's just an indication that a certain substance is involved in elicit trafficking. To what extent, it is difficult to ascertain from STRIDE.

Q Now, also included in the information that you put together, is reflected the information that some MDMA was seized from laboratories, is that correct?

A I'm not sure I understand. Clandestine laboratories

Q Yes.

A Well, the laboratories producing MDMA, I mean making MDMA.

Q Yes.

A Yes,that's correct.

Q Do you recall the number of such laboratories?

JUDGE YOUNG: Documents which you just referred to, and that is Government Exhibit B-2?

BY MR. COTTON:

A Attachment No. 4., page 19, lists at that time 4 laboratories that we were aware of that were producing MDMA. Since that time, we've identified two others, specifically.

Q How many clandestine drug laboratories, to use the DEA terms, does DEA seize each year?

A Oh, the most recent figures are -- these are just

Whereupon,

FRANK L. SAPIENZA

having been previously duly sworn, was called as a witness herein, and was examined and testified further as follows:

CROSS EXAMINATION CONTINUED

BY MR. COTTON:

Q Mr.Sapienza, turning now to the occasions on which you, the occasion in 1979 when you wrote to 17 forensic laboratories and law enforcement agencies, do you recall that letter which you and I discussed this morning?

A Yes, I do.

Q In Attachment 2, to Document B-2, which is the document that you prepared and subsequently transmitted to HEW, you identified 12 letters including the letters that -- some of the letters that responded to your 1979 letter, is that correct?

A Yes, that's correct.

Q But it omits from that compilation, the five letters that responded to you that the laboratory or agency in question had no experience with MDMA. Is that correct?

A That's correct.

Q Why does it omit those letters?

A Because the document was prepared to show the occurrences of MDMA in the elicit drug traffic, and all data relevant to its potential for abuse. Negative letters, I

didn't feel were necessary.

Q. So you presented in this document, only data that would support a finding of abuse potential but you didn't provide any data that tended to negative data, is that correct?

A. That's only partly correct. I mean, if I were to present all negative data regarding everything, it would be voluminous and not shed any -- I didn't think that information would shed any relevant light on whether or not MDMA was abused or to what extent it was.

The data which I received from those letters which said that MDMA was present, in my opinion, were more relevant and shed more light on the fact that MDMA was trafficked or was available on the elicit market.

Q. And you also did not, in your Attachment 2 or in the document itself, reflect the fact that nine respondents to whom you sent letters did not reply at all, nor the fact in connection with the 1982 responses that two of those or possibly three of those were in response to a request for information that had gone to several hundred forensic laboratories. Is that correct?

A. Could you repeat that?

Q. I'm asking -- let me take it one at a time. You also did not include in your Attachment 2 or in that document the fact that nine of the agencies to which you addressed the 1979 letter did not respond at all to your inquiries. Is that

correct?

A. That's correct.

Q. And in reporting the 1982 correspondence, you did not report the fact that that was received in response to a request for information which had gone to several hundred laboratories. Is that also correct?

A. That's right.

MR. COTTON: Your Honor, incidentally, I wonder if we might for the record ask or I would request the Court to ask the Agency to provide for the record the number of the circulation of"Microgram", just so that we can have a firm understanding of how many copies of the newsletter do go out.

JUDGE YOUNG: The circulation as of when?

MR. COTTON: As of 1982 and 1985, which is what the record reflects were the two dates that requests for MDMA, information on MDMA were issued by "Microgram".

JUDGE YOUNG: Can you do that, Ms. Johnson?

MS. JOHNSON: I will make every attempt to find that information and provide it to you, hopefully during these four days.

JUDGE YOUNG: Thank you.

BY MR. COTTON:

Q. Mr. Sapienza, I now would like to turn to some of the scientific literature -- I'm sorry -- excuse me. I want to now turn to another NIDA publication.

application or to get an IND on drugs that have been considered having potential for elicit use, very hard. Having gone through the process on more than one occasion, I can tell you it's the next thing to impossible.

BY MR. STONE:

Q. To your knowledge, is there an investigational new drug application approved for MDMA at this time?

A. I do not know.

Q. You do not know?

A. I do not know.

Q. To your knowledge, is there improved MDA?

A. I don't know.

Q. You do not know?

A. No.

MR. STONE: I have no further questions.

JUDGE YOUNG: Very well. Did you have redirect?

MR. COTTON: Briefly, Your Honor.

JUDGE YOUNG: Yes sir.

REDIRECT EXAMINATION

BY MR. COTTON:

Q. Dr.Zinberg, you just referred to difficulty in obtaining an IND and conducting experiments with Schedule 1 drugs, the way I understood you. Could you describe based on your 20 years of experience, in the field, what you mean by a difficulty in obtaining an IND to carry out experiments on

Schedule 1 drugs?

A. Yes, I certainly can. In 1967, a colleague who had been a medical student, and I decided we wanted to do some controlled experiments on marijuana. Rather simple experiments where we would give marijuana naive subjects and we would use as a control group people who smoke marijuana often before.

And we wanted to really test because there was so much anectodal evidence and no controlled experimental tests of what impact the drug had on various fine physical movements, on memory, on various consciousness change things and so on.

It took us almost two years to get an IND through. We were buffeted back and forth from one agency to the other and it was quite clear that it was the -- that it took laborers that go beyond anything. Okay, that was early. That was in '67 and '68.

So we thought of figured that we broke ground because if there was one thing that the series of papers we wrote showed about this, that it was safe and relatively easy to use the drug experimentally.

And whether our results would be replicated or not, and they were replicated, I'm glad to say, was not as important as the fact that we had indicated that it could be done. And we thought it would become easier to do this.

Then in 1973, again based on anectodal evidence, Emile Frye who is the director of the Sidney Farber Cancer

Center, Steven Salon who is the senior staff person at the Center and myself, decided that we wanted to test marijuana or THC or both on patients that were receiving cancer chemotherapy.

We had some good anectodal evidence that it relieved the nausea of cancer chemotherapy and vomiting, which as you know, is perhaps the most horrible side effect of the drugs. It took us again, almost two years to get an IND.

And the labor, the money it cost was laborious. Then when I had received a government grant to do the study I was telling you about now, and it had been approved by everybody, we wanted to do further work and try to -- we were collecting these subjects. We were interviewing them, and they were a goldmine of opportunity to carry the studies further with virtually no further cost.

We never were able to get an IND. Really tough.

Q Now, Dr. Zinberg, based on your experience and discussions with your colleageus in the field, does this problem, namely the difficulty of obtaining approval to conduct research with humans on Schedule 1 drug, continue to exist today?

A Yes.

Q I want to ask this question without appearing facetious, but why should anyone care? Is research in this area important?

A. Yes. I mean it's important, a whole host of grounds. 1) You know, a lot of people are using these substances and the more we know about them, the better. I mean, we really have to know, not only whether they are therapeutically useful, but to know more about toxicity and you can get that from animal studies.

We really have to have, I think, a very important range of knowledge. I don't know the numbers, but they're enormous. I mean, take marijuana, 50 million people in America have used marijuana.

Those are very big numbers. And to find it so difficult to do research is very hard. But the psychedelics, it's maybe 7 million, I don't know 8 million, or something like that.

But we need to know a lot more. And then secondly, the possibility that these drugs have therapeutic uses, as I say myself have done work which indicated a definitive therapeutic use for marijuana.

And I feel little doubt that there are other usefulnesses for it and other drugs. And we're not exploiting it.

Q. Based on what you've just said, Dr. Zinberg, what would be your expectation of the difference in terms of its impact on research, of placing a drug such as MDMA in the Schedule 1 versus placing it in a lower schedule such as

Schedule 3?

A. It would kill it. There is no research.

JUDGE YOUNG: It would what?

THE WITNESS: It would kill it. It would be the end of it. There's no research being done today on LSD, on MDA, on any of those other drugs.

I don't think there is a single active research project in the United States at this moment, and these are drugs that showed a certain amount of promise. I'm not saying they were panaceas or anything like that.

But I am suggesting that some of the work on terminal patients with LSD, some of the work on alcoholism and drug addiction were extremely interesting pieces of work. These today are very important public health problems.

As soon as they're into Schedule 1, we're finished. Nothing is happening.

BY MR. COTTON:

Q. Finally, I would like to turn to a different subject. As a psychiatrist and based on your professional opinion, is it acceptable medical practice today for a pschiatrist to make a risk benefit assessment and to do decide to administer MDMA in a psychotherapeutic setting for particular classes of patients and for particular indications, disregarding for the moment, if you will, the fact that placement of MDMA in Schedule 1 makes it legally not available to the pschiatric

Tr. 6, October 9, 1985 - Dkt. No. 126

EXCERPT

GRINSPOON CROSS - 90-92

6

UNITED STATES DEPARTMENT OF JUSTICE

Drug Enforcement Administration

- - - - - - - - - - - - - - - -X

In the Matter of: :

Docket No. 84-48

MDMA SCHEDULING :

- - - - - - - - - - - - - - - -X

Room 309 - Courtroom No. 10
United States Claims Court
717 Madison Place, N.W.
Washington, D.C.

Wednesday,
October 9, 1985

The hearing in the above-entitled matter was convened, pursuant to adjournment, at 10:11 a.m.

BEFORE: FRANCIS L. YOUNG
Administrative Law Judge

APPEARANCES:

For the Drug Enforcement Administration:
STEPHEN E. STONE, ESQ.
CHARLOTTE A. JOHNSON, ESQ.
Office of Chief Counsel
Drug Enforcement Administration
Washington, D.C. 20537

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right now, there are a group of -- let's see, one, two, three, four, five senior Harvard researchers plus someone from the National Institute of Health, who decided to get together once MDMA was presented to the research committee, felt that this was something that demanded research as a possible psychotherapeutic agent.

This group was meeting to discuss this issue and then the DEA announced its emergency action on June 31st?

JUDGE YOUNG: July 1st.

MS. JOHNSON: Excuse me --

THE WITNESS: Now, that put an enormous pall on that research. For example, that research may not get under way. For example, there is --

MS. JOHNSON: Could I --

THE WITNESS: Well, I'm trying to answer your question.

MS. JOHNSON: I would like to clarify something because I'm very confused. I was talking about THC. Are you still talking about THC?

THE WITNESS: I'm talking about what I imagine is going on with THC is precisely the same thing that we've experienced. We've never done anything with THC. For example, we had a project -- there are severe obsessive-compulsive patients. An obsessive-compulsive person is a person who has to go through rituals, let's say, has to put on the right shoe

212 times, take it off, put it on 212, and it has to be the left shoe a certain number of times.

These people can spend all day, they're completely crippled. Now, there are patients who have not been helped by anything we can do in psychiatry and they, then, go for brain surgery, psycho-surgery. The particular surgery is a singulatomy (ph).

We, believing that this drug may --

JUDGE YOUNG: Which drug?

THE WITNESS: MDMA, may be helpful to these patients and we have some reason to believe that from the research that was done with LSD and the other psychedelics, but the problems I mentioned make it very difficult -- have been trying to arrange to treat these patients before they go to surgery to see if they would be interested in this kind of -- hopefully, we can get somewhere with some of them and make surgery unnecessary.

And again, the idea of it being Schedule 1 has just put a pall on that. Nobody is willing to undertake the red tape, the enormous time and effort, -- everybody who is a busy researcher doesn't want to spend a lot of time filling out forms and having to change things because the FDA or the DEA says this isn't right or that isn't right.

It's just too much, it will terribly discourage -- I'm terribly afraid that research is not going to go on and

that will be a pity because it's just possible that we might have helped these people who suffer terribly.

BY MS. JOHNSON:

Q Dr. Grinspoon, don't you believe or don't you feel that there is a reason, obviously a reason for certain approvals that need to be granted by the FDA and by the DEA?

A I share the DEA's view that this is a drug which should be controlled. There are very good reasons why it should be controlled, but I believe that the DEA could do this with Schedule 3.

They have all the law they need to interdict traffic or whatever else, with respect to this drug, without putting this kind of a pall on research. This whole MDMA thing is like so many others, it's a risk benefit/analysis. We have to determine what the risk is and what the benefits are.

Now, in Schedule 1, that's going to -- and that risk/benefit analysis is very important. It should be done with the best possible data. If it goes in Schedule 1 or because it is in Schedule 1, we're going to have to rely on street data to make that risk/benefit analysis and that just isn't very good data.

Q Dr. Grinspoon, you're not really responding to my questions and I really would appreciate it if you would listen to what I'm asking and --

A All right, let me try again --

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EXCERPTS

TOCUS CROSS -	62-67, 103-04
DOCHERTY CROSS -	129-132
DOCHERTY REDIRECT -	140-41
LIPTON CROSS -	148 -51
LIPTON REDIRECT -	160-68

Tr. 7

UNITED STATES DEPARTMENT OF JUSTICE

DRUG ENFORCEMENT ADMINISTRATION

- - - - - - - - - - - - - - - -x

In the Matter of: : Docket No. 84-48

MDMA SCHEDULING :

- - - - - - - - - - - - - - - -x

Room 309, Courtroom No. 10
United States Claims Court
717 Madison Place, N.W.
Washington, D.C.

Thursday,
October 10, 1985

The above-entitled matter came on further hearing, pursuant to adjournment, at 10:05 a.m.

BEFORE: HON. FRANCIS L. YOUNG
Administrative Law Judge

APPEARANCES:

For the Agency:

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I N D E X

WITNESSES:	CROSS	REDIRECT	RECROSS
RICHARD P. INGRASCI	19	44	58
EDWARD C. TOCUS	60	--	--
JOHN P. DOCHERTY	120	137	--
MORRIS A. LIPTON	144	160	--

my question before you begin to respond so that the Court Reporter can take down the proceedings accurately.

A Surely.

Q Were you in the Courtroom earlier this morning when there was discussion of the FDA's review of investigational new drug applications associated with Schedule I drugs?

A Yes.

Q As I read your testimony, you or your Division is involved in the review process of any such application for IND's, is that correct?

A That's correct.

Q Could you just describe what the nature of your responsibilities and that of your division are in connection with the receipt of an IND concerning a Schedule I drug?

A Yes. Our Division is the Division of Neuropharmacological Drug Products. We are responsible for the review of all scientific information on drugs that are being studied for marketing that have an effect on the central nervous system. Our Division is divided into three groups: a neurology group which handles the drugs to treat neurological diseases; a psychopharmacology group which handles drugs that are used in treating certain psychiatrically and psychopharmacologically-related

maladies; and the drug abuse staff, the drug abuse group. My group handles and is responsible for any drug that has a potential for abuse. That include the potent narcotics generally. My group is responsible for the narcotic, analgesic agents.

I also have any substance that is in Schedule I or has a potential or is related to a Schedule I substance is referred to my group.

Now, within a group there are three disciplines. There are physicians, there are chemists and there are pharmacologists. Any application of research that is submitted to our Division is reviewed by a physician for the clinical points of view, by a chemist for the chemical control, by pharmacologist for the animal studies related to safety. I am a group leader and I have those disciplines under my supervision.

Q Dr. Tocus, listening to your answer, I heard you say that you conducted those reviews when applications were made to the FDA in connection with marketing. Now, what I'd like to ask is do you also review IND's which are submitted by academic researchers or physician researchers for that matter, who seek to conduct clinical research not related to an effort to market a drug?

A Yes. If a drug is not marketed, the Food and Drug Administration requires that an investigational new

drug application be submitted to the agency for review. And those are the primary applications that we get.

I relate it to marketing because our relationship is generally with the pharmaceutical industry, and most drugs that are being developed for therapeutic purposes are being ultimately developed for general distribution to physicians by the pharmaceutical industry. However, any research on humans for unmarketed drugs must be submitted to the FDA for review and approval.

Q Now, what is the distinction between your review of an application to do research on a Schedule I drug compared with your review of an application to do research on a Schedule II, III, IV or V drug?

A There is no distinction between our review of Schedule I versus Schedule II, III, IV and V. As a matter of fact, if a drug were in Schedules II, III, IV and V, they would generally already be marketed. They would be substances that have already been approved. Most of the drugs that we review have no schedule at all. So the scheduling is not part of our review process. We review all investigational substances irrespective of their control under the Controlled Substances Act.

Q Are you familiar with any legal distinctions that are made in terms of the treatment of such applications for an IND or their relationship to how the DEA treats

registrations to conduct research?

A I don't quite understand what you mean by legal --

JUDGE YOUNG: You'd better rephrase that.

THE WITNESS: -- legal restrictions. I don't understand that.

BY MR. COTTON:

Q What I'm asking is if you are familiar with any different legal requirements that apply to a researcher who seeks to conduct clinical research on a Schedule I drug compared to the legal requirements that apply to researchers who seek to conduct drugs on Schedule II, III, IV or V drugs?

A Yes. Schedule I drugs require an additional registration with the Justice Department. They need a specific registration with the DEA to conduct research with that specific substance.

Q Do they also need affirmative approval from the FDA of their protocol prior to beginning clinical research?

A All investigators need that. That's not peculiar to Schedule I. So that applies to all schedules and the non-scheduled substances. So all research needs our prior approval.

Q Does the FDA have any provision that if a clinician does not hear from the FDA within 30 days from filing its IND, that the clinician is free to proceed?

A Yes, that's true. If they make application -- the process is this. The investigator or researcher makes application to the FDA. It comes into our document room and is date stamped. A copy of that is sent back to the investigator to indicate when we received it. That's the date that the 30 days begin.

We by law have to respond within 30 days of that date to the investigator in terms of the status of his application in our agency. Otherwise, he is free to continue or to initiate his research.

However, if he does initiate his research, and through our review which may be longer than 30 days, we find that there are violations in the Food, Drug and Cosmetic Act, we still have the privilege to stop that study in the interest of protecting the safety and health of the people who are receiving the investigational drug substance.

So you are right, there is a 30-day and we make every attempt to respond within the 30 days. Generally, it is a telephone call.

Q Now, with respect to Schedule I drugs, if a researcher does not hear within 30 days, is it your understanding that he is still free to proceed with his research in the area of Schedule I drugs?

A That's true irrespective of scheduling. That's part of the Food, Drug and Cosmetic Act rather than the

Controlled Substances Act. It's irrespective of scheduling.

Q And can he obtain from the DEA a Schedule I researcher registration in the absence of an affirmative approval of an IND from the FDA?

A Are you asking can he be registered for Schedule I research before being approved for an IND with FDA?

Q Yes.

A Yes. He can be registered without an IND.

Q Now, in terms of the FDA's review of IND's for Schedule I drugs, do you keep records of the IND's that have been approved for Schedule I drugs?

A Yes, we do.

Q And on an annual basis, approximately how many IND's having to do with Schedule I drugs are approved?

A It would be an estimate on my parts in terms of how many IND's are approved in a year. These are new applications.

Q New applications to --

A From new researchers for Schedule I drugs?

Q Yes.

A I would estimate that on the average we would get from 20 to 40 I would say new Schedule I IND applications.

Q And what -- are those kept in FDA files?

it holds up or whether it makes sense.

And what I was addressing in that paper were some of the problems with misconstruing anecdotal data as though it were data that really justified the finding.

Q All right. Now I guess I have two questions that are related to that. I want to take the general first. You described, in effect, a two-stage process, discovery and justification. While science is moving from one to the other, clinicians must make judgments about how to treat individual patients, isn't that right?

A Yes.

Q And it is in that time period when science is moving from discovery to justification that clinicians in effect must rely on the anecdotal evidence that happens to be available in order to make their clinical judgments about how to treat individual patients, is that fair?

A Yes.

Q Now, specifically with respect to MDMA, given your review of Dr. Greer's paper and any other source of information you have about MDMA, do you have a view as to whether it would be useful or important to pursue, in effect, the path that you have just described, namely trying to move from discovery to justification and to conduct clinical trials of the kind that are implicitly described in your testimony on MDMA?

A Yes. I think that it is an interesting compound, one of potentially great importance to the field that ought to be, I think, investigated within a research framework. This is for several reasons. One of the important developments in the field has been the moving together of psychopharmacology and psychotherapy, and their combined use to relieve psychiatric problems.

A drug which could particularly enhance the psychotherapeutic process is sort of at the next stage in that whole development. So that from a scientific development point of view, which is an interesting one especially at this time in the history of the field because it represents a drug which could potentially have an impact on the psychotherapeutic process itself.

Now some of the other drugs that we've been using for the combined use of problems like depression may in fact work that way in the conditions where there is a more effective combined action. We haven't really investigated them particularly from that point of view.

This drug, since it focuses direction in that way, is a useful one because it really points the field where it ought to be headed. It would lead us I think to going back and examining how precisely, for example, a patient who benefits from a combined anti-depressant and psychotherapy does benefit from that combination, whether it

is by the drug affecting different aspects of the problem, or by the two treatments actually developing some kind of synergy, ways of working together.

The other thing that this drug does which is interesting, is that it seems to be affecting a process that occurs between people. And in that way, maybe on the next step in terms of the extension of psychopharmacological treatment to the relief of psychiatric disorders, drugs that by and large we've had developed in the field and that we use now address what we call syndromes.

For example, a psychotic state to be treated by a particular class of drugs, the anti-psychotic agents or manic state by Lithium, or depressed states or anxious states by anti-depressants or anti-anxiety drugs.

Drugs that affect either the personality or interpersonal processes have not been an area that has really been examined in much detail. MDMA is an agent that offers the possibility of moving us into an understanding of some disturbance in interpersonal processes, which is an important aspect of psychiatric disorder, but one which we have really not addressed specifically with our drug treatment.

This has to do with some of the anecdotal reports of the effect of MDMA on what I would call attachment behavior, the degree to which two people form some kind of a

bonding between them, and that's the aspect of it that may have psychotherapeutic importance.

So it could potentially be a very useful drug, and even if it is not useful particularly for therapeutic purposes, a useful one in helping the field develop in a direction which I feel is its next step, both from a psychotherapeutic standpoint, as well as the psychopharmacological standpoint.

Now, since it is important -- this is my personal opinion -- I feel that that has to be done in a very careful manner, because both the scientific credibility of the drug as well as the extent to which it would be used in medical practice would be impaired were that development to not take place in an established -- following an established routine of study.

Q And in order to accomplish the goal that you just stated, namely to carry out this research responsibly and carefully, how would one go about doing that? Do you have a view on that?

A Well, I think that most of the procedures that are actually in place probably make sense. I think it is important to establish the basic safety of the drug through animal testing. This issue came up actually in relationship to whether or not a grant to study the drug might be approved by the National Institute of Medical Health when I

was there. And when we considered that question, we thought it was highly unlikely, I mean virtually that there would be any possibility that an initial review group, which is a group of scientists working in an area, would approve a study where safety testing had not taken place. It's one of their concerns in evaluating an application for approval is the safety of the study for the human beings involved.

So that's essential. That the compound be prepared in a safe manner is also essential.

And then studies would need to be carried out that would help us I think really develop a data base that would be credible. Now why this is important and why for example -- I've heard some of the questions that were asked of Dr. Tocus earlier about the FDA's concern with design of the study -- why that is of importance to the scientific community speaking from time at the NIMH, and now as well, is that there is a great deal of effort, both money and human effort that goes into carrying out a scientific study. It takes a lot of time and human beings are subjecting themselves to risk in order to generate this information.

That being the case, you want to make absolutely certain as best you can given our current knowledge, that the study is conducted in a way that the data will be usable. Because we've had often the experience in science of doing studies and then having the data after many, many years and

all kinds of personalities have been placed in the study, having the data not be usable because there was some flaw in the design of the study.

So that's how I would see this proceed. I think that there is some specific studies that I could outline if you are interested about wherein, how MDMA might be tested I think would be useful for advancing the field. But that generally would be the process that would be undertaken.

Q It is my understanding that as you testified, that the application of the clinical trial methodology to psychotherapy has been one that has been developing over essentially the course of the last 20 years, is that accurate?

A Well, I think psychopharmacology has led the way, and psychotherapy has caught up with that I would say over the last 10 years and the last 5 years in particular.

Q Well, are there difficulties in your opinion in designing research to evaluate a drug such as MDMA as an adjunct to psychotherapy?

A Yeah, there are a lot of problems. There is no such thing as the perfect clinical trial. You just don't have it and there are always compromises based on what you are trying to understand and find out, and those need to be sorted out and worked out, and argued out around the issue of what's the basic hypothesis, because you can in a

clinical situation really control perfectly, so that you have to make compromises in your clinical design.

I do think, however, that it is possible to design, given our current state of knowledge, an investigation of MDMA that would be a scientifically credible one.

Q Do you think that would be a design of a protocol which would require the kinds of compromises and delicate scientific judgments that I take it you were just discussing?

A Yes.

Q Dr. Tocus, are you at all familiar with this --

A Dr. Docherty.

Q -- which is entitled Psychotherapy Research, Methodological and Efficacy Issues, published by the American Psychiatric Association, Commission on Psychotherapy?

A Yes.

Q Does that discuss many of the methodological difficulties in designing studies to evaluate psychotherapy treatment and outcome?

A Yes.

Q And does it -- let me ask, do you agree with this conclusion that even if all the above issues could be adequately resolved, unequivocol conclusions about causal connections between treatment and outcome may never be

possible in psychotherapeutic research? Psychotherapy is a highly complex of interactions that takes place between individuals of an often indeterminant period of time. It is an open-ended, interaction feedback process in contrast to the closed one-way causation that is typical of most laboratory research. Research has not as yet been able to fully document these complex sets of interactions?

A No, no entirely. I take a more optimistic view of research's contribution to it. I think that overall that is probably a reasonable statement of the ability of research to really understand the full nature of psychotherapy and how it works, and that it will really take time to build a basis of scientific information that allows us to understand that process.

I do think, however, it is possible now to define certain questions within psychotherapy practice that can be answered to a satisfactory degree.

Q And in your opinion, it would be possible, utilizing careful scientific judgment to in fact carry out meaningful research on the therapeutic potential of MDMA, is that fair?

A Yes, yes, that's fair.

Q And is it also fair to summarize your previous testimony as stating your belief that it is in fact very important that such research be carried out?

A Yes.

MR. COTTON: I have no further questions, Your Honor.

JUDGE YOUNG: Very well. Did you have redirect, Mr. Stone?

MS. JOHNSON: I have a few questions, Your Honor.

JUDGE YOUNG: Very well, Ms. Johnson.

REDIRECT EXAMINATION

BY MS. JOHNSON:

Q Now, Dr. Docherty, you were aware that MDMA has been given to -- let me back up. You reviewed Dr. Greer's study with 29 patients, did you not?

A Yes.

Q So you are aware that MDMA has been given to individuals in a psychotherapy situation?

A Yes. I mean I've heard that as well. I don't -- yeah. Part of the issue in that paper really had to do with the description of the therapy part of that.

JUDGE YOUNG: Okay. Just take one question at a time.

THE WITNESS: Yes.

BY MR. JOHNSON:

Q All right. Then I was going to ask you what problems you saw with the way that the drug had been given or the way that the paper had been written up regarding the

Based on the reports, if you looked at this in terms of the psychotherapy literature, the psychotherapy research literature, there is an area where this drug might make sense to be used. I mean I must admit to a personal feeling that it was a little too unstructured for my tastes, and --

JUDGE YOUNG: Too what?

THE WITNESS: Too unstructured for my tastes in the way that it was apparently reported. And although there was some steps taken to try to I think be protective of the patient, I would still be a little uneasy about its use in that context.

I do think, though, that the area where it probably has important and testable usefulness is in this issue that's been called the development of a therapeutic alliance. One of the things we know in psychotherapy is that the relationship that develops between the therapist and the patient is extremely important to therapy outcome and accounts for more of the good outcome than any other single variable that's been measured so far, for example whether the therapist uses an analytic technique or a behavioral technique or a Gestalt technique seems to be less important than the alliance that develops between the therapist and patient. And that often takes a great deal of skill depending on the type of patient.

It is also highly predictive of outcome. If a good alliance develops relatively early in the therapy, there will tend to be a good outcome of the therapy. And the drug, the anecdotal reports are of interest in this particular way because they suggest the ability to affect that relationship in a way which might have positive implications for the outcome of the psychotherapy.

There is a study being conducted by Hans Strupp, who is a distinguished investigator in psychotherapy research, of patients who tend to develop hostile relationships with their therapists,have chronic problems but don't seem to be able to be helped by any therapy. And he's developed a specific psychotherapeutic intervention to try to reverse that early hostile alliance and develop a more positive therapeutic one to see whether those patients can be helped.

That same type of group of patients and the measures that are developed in the context of that type of study I think could apply easily to a clinical trial of MDMA which would be in a very restricted context for a particular purpose. And it's the kind of thing that I would think would be the next reasonable step in trying to understand whether this drug has therapeutic usefulness or not.

that worked with LSD, and I think I am the cover and I am responsible for the safekeeping and keeping of the safe, and the dispensing of it and things of that sort.

I have not personally used it, but some of the basic scientists who are working on brain mechanisms have used it and I am reasonably certain that I have an IND for that.

Q What I'm trying to establish is in your statement you say that putting a drug in Schedule I will inhibit research by making it more cumbersome for those who seek an IND. And what I would like you to tell me is the difference between obtaining an IND for the substances, the Hypothalamic substances which are not controlled, and for a substance such as LSD, which is a Schedule I.

A Well, I think it goes with the entire atmosphere, and it will first have to go to the Human Subjects Committee, the Institutional Review Board. If they do innovative, unclassified and you really heavily depend upon your past reputation with that group, you reliability, your credibility, and it will usually go quite rapidly.

That is quite different, even at that level, from someone who might even want to do marijuana research, as a colleague of mine has. And you begin with a prejudice, what kind of kooky stuff are you trying to do now. It can be overcome, but it will usually take several hearings and--

JUDGE YOUNG: It will take what?

THE WITNESS: Several hearings with that group before they will go ahead and let you go on this. I want to correct myself. I recall now I took tetrahydrocannabinol, it was administered to me at a time -- this would have been close to 10 years ago -- at a time when we were interested in developing the oral preparation of tetrahydrocannabinol, so it was mixed with bile salts to make it more soluable, and I took it by mouth, and it was pretty powerful.

BY MS. JOHNSON:

Q So what you were discussing is, as a hold-up factor, is an institutional review committee within the institution that you are working, is that correct?

A Well, that's the first step, yes. There is that hold-up factor.

Q All right. But that is not a Government-created creature, is that true?

A I believe that the Government has -- I'm speculating here. I think the Institutional Review Board of the Human Rights Committee were stimulated, if not ordered, to come into existence for local control. I don't recall the precise mechanism, but they are there.

Q And you have to submit through this Institutional Review Committee any research that you are going to conduct with human subjects, is that correct?

A Yes.

Q All right. And then what would the next step be?

A Well, the next step would then be filing with -- for an IND. And --

Q And -- go ahead, I'm sorry.

A My experience dating back again 20 years to the Psilocybin was discouragement, even before it was before classification. It was hallucinogenic, and they wanted very strong justification for why and what purpose. And since that time, many of my colleagues have told me that if it is a Schedule I drug, and this now involves things like PCP and a few other scheduled ones, that the nuisance, the hassle is such that they would just as soon not do it and go on to other things that are that much easier to do.

Q Now, even with this Psilocybin process, did you eventually -- were you eventually -- was your IND eventually approved?

A That was a colleague's IND that was -- I know he dropped the research. I don't recall whether or not it was approved.

Q But you participated in the research, is that correct?

A I participated as a subject, and I participated somewhat in the design.

Q So you would assume that the IND had been approved

if the research was conducted and you were a subject, is that not correct?

A I guess that is correct, though again 20 years ago it is very hard to recap that. I do have the strong impression that I cannot document from colleagues, who as researchers are always casting about for what can I get a grant on, what is interesting, what is creative, what is productive, what is feasible. And they usually, a clever researcher has his choice of three or four or five different things he may or can do. And if there are roadblocks thrown up one way and it looks like there will be delays and particular hassles, he will tend to avoid it and go on to something else.

Q Would that be the case with any substance that was controlled?

A If by controlled you mean a Schedule I?

Q No, I mean there are Schedules I through V.

A Yes.

Q Would that be the case with any controlled substance, or are you restricting --

A No, I think it would be proportional to the degree of control. A lot of research goes on with Schedule III, IV and V because that is generally a lot easier.

Q Would you say that Schedule II research is as restrictive as Schedule I?

They may affect predominantly one system, but then somehow it sneaks around you and gets to affect another system as well. And I would suspect that the MDMA, that yes, indeed, it would affect both. Certainly amphetamines affect both.

MS. JOHNSON: I don't believe I have any further questions of this witness, Your Honor.

JUDGE YOUNG: Very well, Ms. Johnson. Redirect, Mr. Cotton?

MR. COTTON: Briefly, Your Honor.

JUDGE YOUNG: Yes, sir.

REDIRECT EXAMINATION

BY MR. COTTON:

Q Dr. Lipton, Ms. Johnson made reference to certain papers that you had written on, hallucinogens, and you estimated that you might have written six papers out of 250. Do you remember that dialogue?

A Yes, I remember the dialogue. My figure is not that accurate.

Q Would you simply describe for the record what your primary areas of research interest have been?

A I guess I would in one frame of reference be called a biological psychiatrist, someone who is interested in exploring the biological substrates of psychological processes, which range all the way from what's the biology

of memory, what's the biology of learning. Then to the biology more as a clinician in psychopathological states, like the biology of mood disorders or schizophrenia, even the biology of retardation. That's the general area that I've been in.

Since a good part of that involves pharmacological manipulation, that is a way in which we learn about the biology by introducing drugs to alter the biology, a good part of my research career has been in psychopharmacology, and I was -- I think it was 1980 about -- I was present of the American College of Neuropsychopharmacology, or if you like a reward for many years of work in that.

The third area that I've been interested in is the one that Dr. Docherty referred to, and that is how do drugs and the psychological therapies interact? It's been a very heavily polarized field. If I want to joke about it, I'd say what psychiatry needs is a corpus callosum.

Q What's that again?

A A corpus callosum. That's the portion of the brain which joins the right brain to the left brain. And if you have heard about the split brain preparations that Roger Sperry won a nobel prize for, we act sometimes as if we are split brain preparations. We believe in the effectiveness of psychotherapy, we know that the drugs are

effective with the left brain, then we wonder how do they interact. We still have very little information about how that goes on.

And I think what Dr. Docherty was referring to about the need to try to integrate these two fields is I think a rather pressing need in American psychiatry. I wrote a monograph, what -- 10 years, no,12 years ago, called Pharmacatherapy and Psychotherapy, Principles, Paradoxes and Progress. Well, the paradoxes still remain. There is a little more progress, but it is a field in which there is a great need to move on, and I think it is just beginning to open up, and I would hope that something like MDMA might be helpful in that area.

Q Dr. Lipton, as Deputy Editor of the American Journal on Psychiatry of the American Psychiatric Association, do your duties require you to review a wide range of research in the area of psychiatry?

A Yes, sir.

Q Now, drawing on the experience that you and I have just been discussing, do you regard further research with respect to MDMA to be important?

A Yes, I think it is quite important, particularly in the areas that I have described, in those illnesses in which there are desperate needs and very little effectiveness at the present time.

Q Based on what you know now, do you believe that MDMA has any promise in those areas?

A If I fully believe Dr. Greer and the other reports, anecdotal reports that I have gotten, I would say yes, that it has promise. If you ask me do I take them somewhat with a grain of salt, I take them with a grain of salt, because I take all anecdotal reports with a grain of salt. And I think that this merely accentuates the need for more research, better research, better controlled research, and try to expedite getting a clean answer.

There have been claims of this sort before that bombed. This one may well bomb. I have no idea. But I'd rather see it tried, tried actively, tried vigorously and bomb than have it hang on festering for 10 years or 20 years like some other treatments have in psychiatry where there is just no clear answer and it just goes on and on and on.

Q In your judgment, what effect would placing MDMA in Schedule I have on the expeditious carrying out of such research?

A Oh, I think it would be a very substantial inhibitor. Dr. Docherty, after he finished his testimony, was referring to the fact that if you put it in Schedule I you really socially label it. You in effect say there is enough evidence to be very suspicious of this drug and put it behind bars and be suspect of anyone who is going to use

it and anticipate that there will be a great misuse and so all the precautions in the world, and that makes the investigator suspect. And I think that is one of the many reasons -- there are other reasons as well, by there are not all that many people who are eager to get into this business. There are much more cautious ways of doing research, more productive ways, more profitable ways.

I think this is an area which is important and ought to attract people, but I think that any impediment can be troublesome.

Q Did you and Dr. Docherty discuss what the relative effect on MDMA research would be between putting MDMA in Schedule I versus Schedule II or III?

A No, not specifically.

Q Do you have an opinion on that subject?

A Yes. I think it would be much more effective to have it in Schedule III. I think there might be a little hazard to having it in Schedule III in the sense that it might attract fringe people, but I think that would be a price that is worth paying. And again, the Institutional Review Boards and the like would do it.

I don't know whether it is fair to Dr. Docherty to say what he said in the back, but I don't think it will do any harm. I said to him, "Do you intend to do any MDMA work?" And he said, "Yes." And I said, "In your new

hospital?" And he said, "No." It's a new hospital. It's visible; it's fragile; he doesn't want to be socially labeled. So he will do it in a place where he is better established, where he has been in the past and where he can get away with it. But that's the kind of social fragility I think that comes with using a Schedule I drug.

If it was Schedule III, I suspect he would be much more likely to do it in his new place.

MR. COTTON: Thank you. I have no further questions.

JUDGE YOUNG: Well, Doctor, I take it that you don't put too much stock in this anecdotal experimentation or anecdotal reports that have been coming out, and you think that it is time from what has emerged about MDMA to move into further research that is more structure and more controlled, more scientific programs of research regarding this substance. Am I correct in that?

THE WITNESS: Yes, Your Honor. But let me amplify that. I put stock in the anecdotal stuff for the purpose of opening up new fields. A lot of the fields turn out to be dead ends, but there are some very interesting examples. One of the --

JUDGE YOUNG: I may have misled you. I'm trying to get you to focus on what you think, and I want your opinion with respect to the future course of experimenting

with MDMA. I gather that you think that the point has now been reached that there should be serious scientific control well thought out, research with this substance. Am I correct in that?

THE WITNESS: Yes. I would, not by saying that once in the gate the need for accumulation of more clinical anecdotes. I don't think it is one or the other. I think that the one offers something. The conduct of controlled clinical trials is exorbitantly expensive and very tedious, very time-consuming. I think those are the ones that establish the real science. But the insights and the directions about what controlled clinical trials may still profitably come from the anecdotal type of things, the clinical that concerned physicians want to try.

JUDGE YOUNG: Well, at some point in time before MDMA were to be accepted and giving a stamp of approval and be found, if it ever were to be found, to be truly beneficial and helpful as a therapeutic agent, there would have to be these controlled studies, double blind studies and all the rest of it, right?

THE WITNESS: In general, yes.

JUDGE YOUNG: And specifically for MDMA, isn't that true?

THE WITNESS: Well, I think one would like to see that with all drugs that come out on the market. And if

I were myself, I would like to see it with other procedures as well. Now they still could do that experiment with open heart surgery. Surgeons don't have the same controls that non-surgical physicians do.

If we are working with drugs, we generally have to demonstrate not only that it is safe, effective, but that it is superior to existing products to make it competitive. And it remains a curious business. And in surgery, surgeons don't have to do that. If they say open-heart surgery is good for you, they don't have to compare it with medical treatments, they just go ahead and do it. And that's a curious paradox in American medicine.

JUDGE YOUNG: Thank you, sir. Ms. Johnson, any further questions?

MS. JOHNSON: No, Your Honor.

JUDGE YOUNG: Mr. Cotton?

MR. COTTON: Just one, Your Honor.

JUDGE YOUNG: Yes.

BY MR. COTTON:

Q Dr. Lipton, based on the anecdotal information that you have seen, and contrasting it with your discussion with Judge Young, right now in terms of the need for further clinical double blind studies, would it be -- what is your opinion as to whether prior to July 1 and the scheduling it would have been acceptable medical practice for a

psychiatrist to administer MDMA in one of the contexts -- autistic children or post-traumatic stress syndrome that you identified?

A Oh, I think a concerned physician who had checked it out with his institutional review board and had presented his arguments and his knowledge of the literature would have been justified in using it.

MR. COTTON: I have no further questions.

JUDGE YOUNG: All right. Neither do I. Thank you, Doctor. We appreciate your coming, Dr. Lipton, and giving us the benefit of your testimony. Thank you very much.

THE WITNESS: Thank you, sir.

JUDGE YOUNG: Very well, then. I believe that concludes the schedule for today. Tomorrow we are scheduled to have three witnesses, Dr. Siegel, Dr. Dziewanowska and Mr. Sheahan. So is there anything further before we recess for the evening, Ms. Johnson?

MS. JOHNSON: Two brief things, Your Honor.

JUDGE YOUNG: Yes, Ma'am.

MS. JOHNSON: One is that I spoke to Mr. Angarola, and for the convenience of his witness we have scheduled Mr. Sheahan to be available for cross-examination after Dr. Siegel, and then Dr. -- however you pronounce the name, Dziewanowska.

Tr. 8, October 11, 1985 - Dkt. No. 126

EXCERPT

DZIEWANOSKA CROSS - 119-22

8

UNITED STATES DEPARTMENT OF JUSTICE
DRUG ENFORCEMENT ADMINISTRATION

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In the Matter of: :
: Docket No.: 84-48
MDMA SCHEDULING :
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Friday,
October 11, 1985

U.S. Claims Court
United States Claims Court
717 Madison Place, N.W.
Room 309, Courtroom #10
Washington, D.C.

The above-captioned matter came for hearing before:

FRANCIS L. YOUNG,
Administrative Law Judge

FOR THE DRUG ENFORCEMENT ADMINISTRATION:

STEPHEN E. STONE, ESQUIRE
CHARLOTTE A. JOHNSON, ESQUIRE
Office of Chief Counsel
Drug Enforcement Administration
Washington, D.C. 20537

FOR THOMAS B. ROBERTS, PH.D., GEORGE GREER, M.D., JAMES BAKALAR AND LESTER GRINSPOON, M.D.:

RICHARD COTTON, ESQUIRE
Dewey, Ballantine, Bushby, Palmer & Wood
1775 Pennsylvania Avenue, N.W.
Washington, D.C. 20006

000226

investigator on any clinical trials?

A. At Cornell.

Q. Now in your prior discussion with Ms. Johnson, you identified two primary concerns that you had about a substance which a pharmaceutical company wanted to do research on being placed into Schedule I. As I recall your testimony, one, that it would discourage patients from participating, and two, that it might discourage investigators from participating. Do you recall that testimony?

A. Yes. That's if it's placed in Schedule I.

Q. What -- In terms of your opinion in that regard, what is your judgment? Let's take one at a time, with respect to the reluctance of investigators to participate in a research project that would involve a Schedule I drug based on?

A. Even by the sheer facts, psychological fact, that I would have to say the drug potential belongs to the same category as LSD or heroin. That would keep many investigators away of this program unless compound was of vital importance, and for the healthy volunteers -- By the way, hospital unit where we use mostly healthy volunteer to evaluate some compounds for those to send sign an agreement to voluntary take drug which is defined in this written patient consent. It's absolutely no medical use, no safety and high potential of abuse belonging to the same category

as the drugs I mentioned, I think we want people to get volunteers.

Q. Do you have any doubt about those judgments?

A. About those judgments? No. I can only say that it would be very difficult. It will not be impossible if we had analgesic scheduled on Schedule I and it was very important for the terminal cancer patients -- those patients -- those studies could be done. But if it's new anticonvulsant or if it's new antidepressant, that would be very difficult.

Q. Now you went so far in your discussion with Ms. Johnson, as I recall your testimony, as saying that if you, meaning Hoffman-La Roche had a substance in Schedule I, placed in Schedule I, that your company would not develop it. Do you recall making that statement?

A. Unless it was a life-saving substance, probably would not be considered by the company.

Q. Now you're saying that obviously as someone who has the capacity as the Director of Clinical Research and Assistant Vice President of a major pharmaceutical house -- My question is: Is that a judgment that you think would be shared by colleagues of yours who hold similar positions in those companies?

A. If I can ask for clarification, are your saying if our new investigational substance was to be scheduled on Schedule I during the evaluation process would we drop it?

Is that your question?

Q. I was trying --

A. Or would we have a drug scheduled in Schedule I?

Q. I'm sorry. I was simply trying to paraphrase your testimony. Maybe the easiest way to do it is to just to ask you to restate what you view is. Are there circumstances where your company in your judgment did not go forward with the development of a drug because it was either originally in Schedule I or was placed in Schedule I at some critical point of your decision-making process?

A. If we believed that the substance should be in Schedule I, if we believed that substance had a high potential for abuse and no medical use, we would have absolutely no incentive in going ahead ourselves.

Q. All right. But if there was a substance which you believed such as an antidepressant or had some potential to be an antidepressant and that substance was placed into Schedule I, would you then proceed to run the clinical trials to try to receive FDA approval to try to market it?

A. As I said, I believe that it would be very difficult to conduct all the expense in five to seven years, clinical trials with a substance remaining in Schedule I. It would have to be a really breakthrough to warrant it.

Q. Now my question was: Do you believe that that perspective which you've just expressed is unique to yourself

or to a particular philosphy of Hoffman-La Roche or is it one that you base on your experience and conversation with your counterparts and other pharmaceutical companies would be more broadly held within the pharmaceutical industry?

A. I don't believe it's unique.

JUDGE YOUNG: What's your answer?

THE WITNESS: I don't believe my attitude is unique or represents exclusively Hoffman-La Roche.

BY MR. COTTON:

Q. Now, Dr. Dziewanowska, in your testimony on the first page in paragraph number 5, you make the statement that it is your professional scientific opinion that substances which are the subject of investigational new drug exemptions and even substances at the pre-IND state of development must be considered as belonging to the category of substances having currently accepted medical use and treatment in the United States, as that phrase is used in the Federal Controlled Substances Act, since they have the potentiality for becoming approved drugs. I'd like to ask what you mean by even substances at the pre-IND stage of development.

A. What do I mean by substances in pre-IND?

Q. Yes.

A. It is the -- My evaluation is the clinical which underwent animal testing to the fine pharmacological activity to the fine toxicology which is ready to have -- at the state

Tr. 9, November 1, 1985 - Dkt. No. 149

EXCERPTS

TOCUS CROSS	-	35-36, 44, 50, 67-68, 79-80

UNITED STATES DEPARTMENT OF JUSTICE

DRUG ENFORCEMENT ADMINISTRATION

- - - - - - - - - - - x

In the Matter of: :

: Docket No. 84-48

MDMA SCHEDULING :

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Courtroom No. 10
United States Claims Court
717 Madison Place, N.W.
Washington, D.C.

November 1, 1985

The hearing in the above-entitled matter commenced at 10:12 a.m.

BEFORE:

FRANCIS L. YOUNG
Administrative Law Judge

APPEARANCES:

For the Drug Enforcement Administration:

STEPHEN E. STONE, ESQ.
CHARLOTTE A. JOHNSON, Attorney at Law
Office of Chief Counsel
Drug Enforcement Administration
Washington, D.C. 20537

For Thomas B. Roberts, Ph.D., George Greer, M.D., James Bakalar and Lester Grinspoon, M.D.:

RICHARD COTTON, ESQ.
Dewey, Ballantine, Bushby, Palmer & Wood
1775 Pennsylvania Avenue, N.W.
Washington, D.C. 20006

or enclosed to the letter and is an evaluation of that particular recommendation.

Q Who prepared those documents?

A I can't say for sure who prepared these two final documents. My office can, and often does, prepare draft documents, stamped "Draft," and I believe that the Office of the Assistant Secretary, the final documents are prepared on their equipment, on their stationery. I can't say whether these are the exact documents that my office prepared, because ours have signature blocks on the bottom which would indicate who prepared it. These are the finals.

Q In terms of the document -- let me start again -- did you or your office prepare documents which were forwarded to the Office of the Commissioner of the Food and Drug Administration and thereafter to the Assistant Secretary for Health, analyzing the recommendation of the DEA to control MDMA?

A Yes.

Q Where are those documents -- let me ask the question differently -- are the two documents that you are looking at, B-3 and B-4, the documents that you prepared and forwarded to the Commissioner and then on to the Assistant Secretary with respect to the MDMA scheduling recommendation of DEA?

A I would think they are. I just can't say that

these are the ones because they are not marked "Draft" anymore. I would think these are the final copies of the ones that my office prepared, but I can't say that for certain because I don't have them.

Q Did you prepare documents that are different from the ones you are looking at?

A No, I would not have prepared any document that are different.

Q I don't mean to flog a dead horse, Dr. Tocus, but my question is, are these the documents which reflect the analysis of your office which was forwarded to the Commissioner of the FDA and then to the Assistant Secretary for Health, and on the basis of which those individuals acted to carry out their statutory responsibilities with respect to the evaluation of DEA's scheduling recommendation for MDMA?

A Yes.

Q They are?

A They are.

Q Thank you.

Other than those two documents, did you prepare any other documents reflecting any analysis of any kind with respect to the scheduling recommendation on MDMA?

A The only other document that was prepared was an 8-factor analysis on MDMA that was part of this package,

those three documents within your office?

A I personally prepared our revision of the control recommendation.

JUDGE YOUNG: That is this multi-page document, 22 pages long or thereabouts?

THE WITNESS: Yes.

JUDGE YOUNG: All right, sir.

THE WITNESS: I personally prepared that. I believe I also prepared the evaluation that is attached to that.

JUDGE YOUNG: Is that Government's Exhibit B-4?

THE WITNESS: Yes.

JUDGE YOUNG: Thank you.

THE WITNESS: I am not sure whether I personally prepared the letter which is signed, addressed to Mr. Mullen. I just don't recall having written this particular document, but my office, either I or my assistant would have written a draft letter.

JUDGE YOUNG: You are talking about Government's Exhibit B-3 at this point?

THE WITNESS: Yes.

JUDGE YOUNG: Thank you.

BY MR. COTTON:

Q Thank you. Now, with respect to Greer-Grinspoon Exhibit 54, which is the note from the Acting Commissioner

think the NIDA people were reiterating to us, that there was a lack of data, the data did not exist. I believe that is the issue. If we had been able to find additional information, then that would have been taken in, but the information which DEA had supplied us seemed to be the totality as far as we or NIDA was aware of that particular factor, its actual or relative potential for abuse. At this time, there was just no information. We had no information in our files and I don't believe NIDA had information in their files. That is why NIDA is saying that the direct evidence is not substantiated based on the data provided.

There was not direct evidence, this didn't exist. Nobody had done the studies.

JUDGE YOUNG: Mr. Cotton, your half-hour is just about up, but I realize that you are having to cope with a situation where you have documents now you did not have before. So I will ask you how much longer you anticipate your cross-examination will continue.

MR. COTTON: I would anticipate for approximately another 15 or 20 minutes, Your Honor, and I would request that my time be extended for that period.

JUDGE YOUNG: Carry on.

BY MR. COTTON:

Q Dr. Tocus, are you familiar with the National Institute of Mental Health?

Q Dr. Tocus, at the time that you prepared the document, was it your understanding that if a drug did not have an NDA approved by the FDA, or was not otherwise legally marketed interstate, if it was in that category, and if you wanted to recommend that the drug be scheduled, did you have a view as to whether you could recommend a drug to be scheduled in a schedule lower than Schedule I?

A My view at the time was that if it was not approved by the Food and Drug Administration, that the only alternatives were Schedule I or no schedule at all.

Q So that in preparing your document, if you had come to a conclusion that it should be scheduled, you really had no alternative other than to recommend that it be placed in Schedule I in your view, is that correct?

A That is correct.

Q Now, a final question, Dr. Tocus. Turning to what has been marked as Greer-Grinspoon Exhibit 54, which is the note from the Acting Commissioner of Food and Drug to the Assistant Secretary of Health, that note recommends that MDMA be placed in Schedule I of the Controlled Substances Act because MDMA has a significant potential for abuse, isn't that the way that note reads?

A Yes, it does.

Q Now, something that has a significant potential is not clearly a substance that has a high potential for

abuse, isn't that right?

A I don't know, because this is now a judgment of whether high is significant or not.

Q But the one thing that we can be certain of, Dr. Tocus, is that the Commissioner or Acting Commissioner of the Food and Drug Administration, when he made his recommendation to the Assistant Secretary for Health, did not use the word "high" and did not in terms find that MDMA had a high potential for abuse, isn't that right?

A He did not use the term "high," that is right. I don't know whether the word "significant" correlates with the word "high" or not. I just cannot say what his intention was there.

MR. COTTON: I have no further questions, Your Honor.

JUDGE YOUNG: Very well, sir.

Do you have redirect from the Agency?

MR. STONE: Yes, we will, Your Honor.

JUDGE YOUNG: How long do you estimate that will take?

MS. JOHNSON: I would say at least half an hour, Your Honor, and I would respectfully request at least a few minute recess at this time.

JUDGE YOUNG: Yes, I think perhaps that is what we should do, take a brief recess rather than recess now

A Yes.

Q Did you find any scientific literature other than the literature that was mentioned in the DEA document?

A No.

Q Now, did you consult with individuals in FDA and NIDA about the scheduling before you prepared the two-page document that is Government's Exhibit B-4?

A Yes.

Q How did you do this?

A Face-to-face discussions.

Q And you received an opinion from the National Institute on Drug Abuse prior to preparing your evaluation?

A Yes.

Q What was this opinion that you received from them?

A That they concurred that MDMA should be placed in Schedule I.

Q Now, you indicated in your testimony that, in this particular instance, there was no Advisory Committee consideration of the scheduling of MDMA, is that correct?

A That is correct.

Q Can you tell me why that was the case?

A There are two basic reasons, two main reasons that we did not go to the Advisory Committee. One, this particular issue seemed so clear to us. We had no information in our data bases. The substance appeared to be similar to an

already controlled substance. Our ultimate course of action seemed very clear to us, that we didn't see the controversy that would require us to go to an Advisory Committee. That was one reason.

The other reason was that we were requested to expedite a response to the request from DEA and to go to an Advisory Committee would probably have delayed the recommendation for a matter of four to six months before we could get all the necessary procedures to go through, hold the committee, and then do all the work that results from holding an Advisory Committee meeting would have delayed the recommendation for quite a long time.

We didn't feel that this issue warranted that type of activity.

Q Now, you have been involved in several scheduling reviews, is that correct?

A Yes.

Q Are there occasions when a proposed scheduling action does go to an Advisory Committee?

A Oh, yes.

Q Who makes these kind of decisions?

A We make them internally. We make that decision in the division.

Q Would you say that this is just one of the tools that you have at your disposal to evaluate a recommendation

EXHIBITS

GRINSPOON

GG-15
GG-38
GG-54
GG-55
GG-57

DEA

B-1
B-2
B-3
B-4
B-14

Legislative Counsel of California

BION M. GREGORY

Sacramento, California
May 26, 1981

Honorable John R. Garamendi
Senate Chamber

Sherman Food, Drug, and Cosmetic Law - #8182

Dear Senator Garamendi:

QUESTION

Does the Sherman Food, Drug, and Cosmetic Law prevent a physician from prescribing, or a pharmacist acting pursuant to the order of a physician from dispensing, a drug not approved in a federal or state new drug application?

OPINION

The Sherman Food, Drug, and Cosmetic Law does not prevent a physician from prescribing, or a pharmacist acting pursuant to the order of a physician from dispensing, a drug not approved in a federal or state new drug application.

ANALYSIS

Initially, we note that in view of your specific question, we have not, in this opinion, considered whether there is any state law, other than the Sherman Food, Drug, and Cosmetic Law, which would prevent a physician in any case from prescribing or administering a drug not approved in a federal or state new drug application.

Exh. GG-15

The Sherman Food, Drug, and Cosmetic Law (Division 21 (commencing with Section 26000) of the Health and Safety Code,[1] includes within its scope or regulation the selling, dispensing, giving away, supplying, or applying of any drug in California (see Sec. 26050, H.& S.C.). Under Section 26670, a "new drug" generally may not be sold, delivered or given away unless a new drug application has been filed with, and approved by, the state or federal government.[2]

A "new drug" is defined, for the purposes of the Sherman Food, Drug, and Cosmetic Law, by Section 26021, as follows:

> "26021. 'New drug' means either of the following:
>
> "(a) Any 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 or advertising thereof.
>
> "(b) Any 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."

Section 26021 expressly includes as new drugs only those drugs that are advertised or labeled to prescribe, recommend, or suggest conditions for use which (1) are not

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1 All section references are to the Health and Safety Code, unless otherwise noted.

2 Certain drugs are exempted from the requirement (see Sec. 26680).

generally recognized as safe or effective applications by experts or (2) have received that recognition as the result of investigational use, but have not been employed to a material extent or for a material time outside of the investigational context. Thus, the section clearly and unambiguously defines "new drug" in relation to the conditions for use prescribed, recommended, or suggested in the labeling or advertising of a drug, rather than the actual conditions of use by the professional practitioner.

The definition of "new drug" contained in Section 26021 is modeled after the definition of "new drug" contained in the federal Food, Drug, and Cosmetic Act (see subsec. (p), Sec. 321, Title 21, U.S.C.). The federal Food, Drug, and Cosmetic Act provides for a system of premarketing clearance for drugs introduced in interstate commerce, based upon proven safety and effectiveness (Weinberger v. Hynson, Westcott, and Dunning, Inc., 37 L. Ed. 2d 207, 213-214). In interpreting the federal law, a federal district court has held "... the Food and Drug Administration does not have jurisdiction to regulate the administration of a drug by a physician (F.T.C. v. Simeon Management Corporation (N.D. Calif.), 391 F. Supp. 697, 706. The Food and Drug Administration of the United States Department of Health and Human Services has also informed us that, in its opinion, it does not have the authority under the federal Food, Drug, and Cosmetic Act to prevent a physician, or a pharmacist acting pursuant to the order of a physician, from prescribing a drug not approved in a federal new drug application.

We note that there are differences in the prohibitions respecting new drugs between federal and state law. The relevant provisions of federal law generally prohibit only introduction, or delivery for introduction, into interstate commerce of unapproved new drugs (subsec. (a), Sec. 355, Title 21, U.S.C.), whereas state law generally prohibits any sale, delivery, or gift of an unapproved new drug (Sec. 26670).

However, the Legislature adopted the essence of the federal definition of "new drug." It cannot be assumed that the Legislature was ignorant of the consequences of the language it used (County of Santa Clara v. Hall, 23 Cal. App. 3d 1059, 1065; see also County of Los Angeles v. Graves, 210 Cal. 21, 24). If the Legislature had intended to provide for more than premarketing clearance for new drugs, we think it would not have employed language so similar to that in the federal Food, Drug, and Cosmetic Act.

In our opinion the state law was designed to fill the hiatus in federal law with respect to drugs which are manufactured and marketed solely in intrastate commerce. Although, as noted above, the prohibitions of Section 26670 are different from those of the federal new drug provisions, such difference is necessitated by the application of state law to intrastate transactions. The prohibitions of Section 26670 are the analogue of the prohibitions of federal law discussed above, but are applicable to the appropriate intrastate transaction. In all other relevant respects, the federal and state schemes for regulation of new drugs are essentially parallel.

In our view there is an unambiguous statutory definition of the term "new drug" in Section 26021, which is determinative of the issue in question. The prohibitions contained in Section 26670 relate to new drugs; the section does not itself define "new drug." What is a "new drug" for purposes of Section 26670 is defined by Section 26021, which, as discussed above, makes that status dependent upon the advertising or labeling (or proposed advertising or labeling) of a drug.

Additionally, nothing in the Sherman Food, Drug, and Cosmetic Law expressly prohibits a physician from prescribing a drug not approved by a state or federal new drug application, although the act contains numerous provisions concerning prescribing and prescriptions. Where a physician issues a prescription filled by an independent pharmacist, he does not, in the literal sense, himself sell, deliver, or give away the drug as specified in Section 26670 (see Sec. 26050). An omission of an act from a penal statutory provision, such as Section 26670 (see Sec. 26801), evinces a legislative purpose not to punish the omitted act (In re James M., 9 Cal. 3d 517, 522).

Furthermore, to apply Section 26670 to a physician in the event the physician treats a patient with a "new drug," the physician would be required to comply with the new drug provisions of the Sherman Food, Drug, and Cosmetic Law. Those applicable sections require (1) new drug applications for approval of new drugs (Sec. 26670); (2) six-month waiting periods on applications (Sec. 26671); (3) hearings (Sec. 26671); (4) submitting reports of investigation and testing (Sec. 26672); (5) labeling and advertisement

(Sec. 26672); (6) manufacturing methods, facilities, and controls (Sec. 26672); (7) maintaining clinical records pending approval (Sec. 26674), and department orders withdrawing approval of applications (Sec. 26675). The intent of the Sherman Food, Drug, and Cosmetic Law is, we think, to regulate the commercial activities of persons who engage in the manufacturing of drugs, rather than to regulate a physician treating a patient on an individual basis.

In this regard, Section 26666 authorizes a physician to personally furnish his own patients with drugs that are necessary in the treatment of the condition for which the physician attends those patients. It is our opinion that Section 26666 confers the right of a physician to exercise his or her professional discretion when providing drugs in a therapeutic setting. Section 26666 makes no distinction between new drugs and other drugs, but merely refers to drugs which are necessary in the treatment of the condition (see also, Sec. 4051, B.& P.C.).

The State Department of Health Services has also adopted regulations relating to "new drugs." Section 10416 of Title 17 of the California Administrative Code reads as follows:

> "10416. Section 26666 of the Health and Safety Code shall be construed only as applying the same exemptions to labeling requirements for drugs dispensed by a physician, dentist, podiatrist, or veterinarian, as are provided for drugs sold by filling or refilling a written or oral prescription of such practitioner and shall not provide any exemption from the requirements of Section 26670 (new drugs) of the Health and Safety Code or from the requirements of Chapter 7 (commencing with Section 1700) of Division 2 of the Health and Safety Code (Cancer Law)."

However, an administrative officer may not make a rule or regulation that alters or changes the terms of a legislative enactment (Whitcomb Hotel, Inc. v. Cal. Emp. Com., 24 Cal. 2d 753, 757). Administrative regulations that violate acts of the Legislature are void, and no protestations that they are merely an exercise of administrative discretion can sanctify them; they must conform to the legislative bill

to preserve an orderly system of government (Morris v. Williams, 67 Cal. 2d 733, 737). In our opinion Section 10416 of Title 17 of the California Administrative Code, relating to the furnishing of new drugs by a physician within the meaning of Section 26670, conflicts with the provisions of the Sherman Food, Drug, and Cosmetic Act discussed above, and therefore is unenforceable and void.

We think that if the Legislature had intended to preclude physicians from utilizing drugs not yet approved by either the state or federal government as safe and effective, the law would have been drafted to prohibit physicians from prescribing, as well as dispensing, those drugs. It would be illogical, in terms of rational legislative policy directed towards protection of the public from unsafe or ineffective drugs, to distinguish for that purpose on the basis of whether a physician or a pharmacist dispenses an unsafe or ineffective drug. That Section 26670 contains no express prohibition against prescribing a new drug is a further indication that the new drug provisions of the Sherman Food, Drug, and Cosmetic Law were not intended to regulate the practice of medicine, but only to provide a system of premarketing clearance for drugs based upon preapproval of labeling and advertising claims respecting safety and effectiveness.

Therefore, it is our opinion that the Sherman Food, Drug, and Cosmetic Law does not prevent a physician from prescribing, or a pharmacist acting pursuant to the order of a physician from dispensing, a drug not approved in a federal or state new drug application.

Very truly yours,

Bion M. Gregory
Legislative Counsel

By Sandra Hughes
Sandra Hughes
Deputy Legislative Counsel

SH:kca

OFFICE OF THE ATTORNEY GENERAL
State of California

EVELLE J. YOUNGER
Attorney General

OPINION

of

EVELLE J. YOUNGER
Attorney General

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Deputy Attorneys General

CV 76/212
CV 77/236

MAY 2, 1978

THE HONORABLE CHARLES V. CUMMINS, PRESIDENT OF THE CALIFORNIA STATE BOARD OF PHARMACY, has requested an opinion on the first and second questions; THE HONORABLE WILLIAM CAMPBELL, SENATOR FOR THE 33RD DISTRICT, has requested an opinion on the third and fourth questions:

1. May a pharmacist compound and dispense, pursuant to an individual prescription order of a physician, dentist, podiatrist, or veterinarian, materials for an individual patient's needs which materials, although not specifically banned, have not received a clearance from the Federal Food and Drug Administration or approval from the State Department of Health and which otherwise may be "new drugs" within the meaning of Health and Safety Code section 26021, subdivision (a) and (b), and 21 U.S.C.A., section 321, subdivision (p), subparts (1) and (2), and the commercial sale of which would be prohibited under Health and Safety Code section 26670 and 21 U.S.C.A., section 355?

2. May a pharmacist lawfully compound and dispense on the written prescription of a dentist, "new drugs" or materials in formula similar to the products N-2 or RC-23 which have not received an investigation new drug (IND) or new drug approval (NDA) clearance from the Federal Food and Drug Administration or the State Department of Health, and the commercial sale of which is prohibited?

3. Does the Sherman Food, Drug, and Cosmetic Law prevent a physician from prescribing or administering a drug for a condition not specified in the drug's advertising which has been approved in a federal or state new drug application?

4. Do a physician's representations to his patient governing the effectiveness of a drug in treating a particular disease of the patient constitute a violation of section 26463 of the Health and Safety Code?

The conclusions are:

1. A pharmacist may compound and dispense, pursuant to an individual prescription order of a physician, dentist, podiatrist, or veterinarian, materials for an individual patient's needs so long as the component elements of such materials in any combination or singly have not been banned by state or federal law or regulation, even though such materials, if not dispensed pursuant to a prescription, may be considered "new drugs" within the meaning of Health and Safety Code sections 26021, subdivisions (a) and (b), and 21 U.S.C.A., section 321, subdivision (p), subparts (1) and (2), and their commercial sale would be prohibited under Health and Safety Code section 26670 and 21 U.S.C.A., section 355, more precisely section 331, subdivision (k).

2. A pharmacist may compound and dispense pursuant to the written prescription of a dentist, for an individual patient's needs, materials in formula similar to the products N-2 or RC-2B even though such materials have not received an investigational new drug (IND) or new drug approval (NDA) clearance from the Federal Food and Drug Administration or the State Department of Health, and even though the commercial sale of such materials may be prohibited, provided that the component elements of such materials in any combination or singly have not been banned by state or federal law or regulation.

3. The Sherman Food, Drug, and Cosmetic Law does not prevent a physician from prescribing or administering a drug for a condition not specified in the drug's advertising approved in a federal or state new drug application.

4. A physician's representations to his patient governing the effectiveness of a drug in treating a particular disease of the patient do not constitute a violation of section 26463 of the Health and Safety Code.

CV 76/21..
CV 77/236

ANALYSIS

Health and Safety Code section 26670 provides that "[n]o person shall sell, deliver, or give away any new drug or new device unless. . ." it has been approved by the Secretary of Health, Education and Welfare (21 U.S.C.A. § 355) or the California Department of Health (Health & Saf. Code § 26670).

Under the federal law, a new drug may not be introduced or delivered for introduction into interstate commerce absent an approval of a new drug application (21 U.S.C.A. § 355), or absent an exemption based upon its being used solely for investigational use (21 U.S.C.A. § 355, subd. (i)). (See Health & Saf. Code §§ 26668-26669 for provisions of California law relating to experimental use of drugs.)

The first two questions presented seek to determine, in essence, whether a licensed pharmacist violates Health and Safety Code section 26670 and/or 21 U.S.C.A. section 331 by selling or delivering a new drug pursuant to an order (prescription) of a physician, dentist, podiatrist, or veterinarian, licensed in accordance with the laws of the State of California.

The Federal Food, Drug and Cosmetic Act (21 U.S.C.A. §§ 301-392) and the California Sherman Food, Drug and Cosmetic Law (Health & Saf. Code §§ 26000-26851) 1/ are applicable to drugs. The California Pharmacy Law (Bus. & Prof. Code §§ 4000-4416) is applicable to licensed pharmacists.

The Federal Food, Drug and Cosmetic Act (hereinafter called the Federal Act) is a congressional implementation of authority granted to it by the commerce clause of the Federal Constitution. The California Sherman Food, Drug, and Cosmetic Law is a legislative enactment pursuant to an exercise of the police power vested in it by the California Constitution. (See Williamson v. Lee Optical Co. (1955) 348 U.S. 483; Berman v. Porter (1954) 348 U.S. 26.) It is well established that the states may enact regulatory laws dealing with local aspects of interstate commerce, if they do not unreasonably burden that commerce. (See Huron Cement Co. v. Detroit (1960) 362 U.S. 440.)

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1. All unidentified section references are to the Health and Safety Code, more particularly to the Sherman Food, Drug and Cosmetic Law, as contained in the Health and Safety Code.

The State of California has the power to regulate, through the exercise of its police power, the practice of medicine, dentistry and pharmacy within the state (see e.g., Rosenblatt v. Cal. St. Bd. of Pharmacy (1945) 69 Cal.App.2d 69) and the state may regulate the administration of drugs (Blinder v. Division of Narcotic Enforcement (1972) 25 Cal.App.3d 174), including outright banning of such distribution (see California Optometric Assn. v. Lackner (1976) 60 Cal.App.3d 500).

The primary and controlling consideration in the construction of a statute is the determination of and the giving of effect to the legislative intent behind the statute. (Great Lakes Properties, Inc. v. City of El Segundo (1977) 19 Cal.3d 152, 163; Select Base Materials v. Board of Equal. (1959) 51 Cal.2d 640, 645; Steilberg v. Lackner (1977) 69 Cal.App.3d 780, 785.)

In determining the legislative intent, the court turns first to the words used in the statute. (Moyer v. Workman's Comp. Appeals Bd. (1973) 10 Cal.3d 222, 230; Steilberg v. Lackner, supra, 69 Cal.App.3d at p. 785.) The court is required to give effect to the statutes according to the usual ordinary import of the language, significance being given to every word, phrase, sentence and part of an act in pursuance of the legislative purpose. (Moyer v. Workman's Comp. Appeals Bd., supra, at p. 230; Steilberg v. Lackner, supra, at p. 785.)

Where the language of a statute is clear, its plain meaning should be followed. (Great Lakes Properties, Inc. v. City of El Segundo, supra, 19 Cal.3d at p. 155.) If such is the case, the sole function of the courts is to enforce the statute according to its terms. (Leroy T. v. Workmen's Comp. Appeals Bd. (1974) 12 Cal.3d 434, 438.)

Thus the initial question becomes:

Is a pharmacist subject to the Sherman Food, Drug and Cosmetic Law? As stated earlier, section 26670 provides that:

> "No person shall sell, deliver, or give away any new drug or new device unless it satisfies either of the following:
>
> "(a) It is a new drug, and a new drug application has been approved for it and such approval has not been withdrawn, terminated, or suspended under Section 505 of the federal act (21 U.S.C., Sec. 355); or it is a new device for

which a premarket approval application has been approved, and such approval has not been withdrawn, terminated, or suspended under Section 515 of the federal act (21 U.S.C., Sec. 360e).

"(b) The department has approved a new drug or device application setting forth all of the following information:

"(1) Full reports of investigations which have been made to show whether or not such new drug or device is safe for use or whether such new drug or device is effective in use under the conditions prescribed, recommended, or suggested in the labeling or advertising of the new drug or device.

"(2) A full list of the articles used as components of such new drug or device.

"(3) A full statement of the composition of such new drug or device.

"(4) A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such new drug or in the case of a new device, a full statement of its composition, properties, and construction and the principles of its operation.

"(5) Such samples of such new drug or device and of the articles used as components of the drug or device as the department may require.

"(6) Specimens of the labeling and advertisements proposed to be used for such new drug or device.".

There can be no question but that in the context of all of the provisions of the Sherman Food, Drug, and Cosmetic Law a pharmacist is a "person" within the meaning of section 26670. This conclusion is based upon the following statutes:

Section 26024 provides that:

"'Person' means any individual, firm, partnership, trust, corporation, company, estate, public or private institution, association, organization, group, city, county, city and county, political subdivision of this state,

other governmental agency within the state, and any representative, agent, or agency of any of the foregoing."

Furthermore, section 26050 provides that:

"The provisions of this division regarding the selling of any food, drug, device, or cosmetic include, but are not limited to, all of the following:

"(a) The manufacture, production, processing, and packing of any food, drug, device, or cosmetic.

"(b) The exhibition, offer, possession, or holding of any food, drug, device, or cosmetic for sale, dispensing, giving, supplying, or applying in the conduct of any establishment.

"(c) The sale, dispensing, giving, supplying, or applying of any food, drug, device, or cosmetic in the conduct of any establishment." (Emphasis added.)

The State Pharmacy Law (Bus. & Prof. Code §§ 4000-4416) provides in part that:

"Except as otherwise provided in this chapter, it is unlawful for any person to manufacture, compound, sell or dispense any drug, poison or chemical, or to dispense or compound any prescription of a medical practitioner unless he is a registered pharmacist under the provisions of this chapter." (Bus. & Prof. Code § 4050.) (Emphasis added.)

"'Furnish' means to supply by any means, by sale or otherwise." (Bus. & Prof. Code § 4044.5.) (Emphasis added.)

"'Dispense' means the furnishing of drugs upon a prescription from a physician, dentist, podiatrist or veterinarian." (Bus. & Prof. Code § 4049.) (Emphasis added.)

Returning to the provisions of the Sherman Food, Drug, and Cosmetic Law, section 26027 provides that:

"'Prescription' means an oral order given individually for the patient for whom prescribed

directly from the prescriber to the furnisher or indirectly by means of a written order signed by the prescriber which bears the name and address of the prescriber, the license classification of the prescriber, the name and address of the patient, the name and quantity of drug or device prescribed, the directions for use, and the date of issue." (See also Bus. & Prof. Code § 4036.)

Section 26660 specifies the categories of drugs which shall be sold only upon a written or oral prescription of a practitioner licensed by law to prescribe such a drug, thus implicitly regulating the acts of a licensed pharmacist in dispensing drugs. Furthermore, section 26662 sets forth certain labeling requirements which a pharmacist must adhere to when selling or dispensing a prescription drug, as follows:

"Any drug or device sold by filling or refilling a written or oral prescription of a practitioner licensed to prescribe such drug or device shall be exempt from the labeling requirements of Sections 26631, 26632, 26634, 26635, 26636, 26637, 26638, 26639, 26640, 26642, 26646, and 26647, if the drug or device bears a label displaying all the following:

"(a) Except where the prescriber orders otherwise, either the manufacturer's trade name of the drug, or the generic name and the name of the manufacturer. Commonly used abbreviations may be used. Preparations containing two or more active ingredients may be identified by the manufacturer's trade name or the commonly used name or the principal active ingredients.

"(b) The directions for the use of the drug or device.

"(c) The name of the patient.

"(d) The name of the prescriber.

"(e) The date of issue.

"(f) The name, address and prescription number of the furnisher.

"(g) The strength of the drug or drugs prescribed.

"(h) The quantity of the drug or drugs prescribed.

"(i) The expiration date of the effectiveness of the drug or device if such information is included on the original label of the manufacturer of the drug or device.

"The exemption shall not apply to any drug or device dispensed in the course of the conduct of a business of dispensing drugs or devices pursuant to diagnosis by mail, or to a drug or device dispensed in violation of Section 26660."

The provisions create no ambiguity; they allow for one interpretation only: the provisions of the Sherman Food, Drug, and Cosmetic Law apply to pharmacists. A pharmacist is subject to the provisions of section 26670 to the extent that he or she dispenses a new drug and therefore, he or she may dispense a new drug only as permitted by the provisions of the Sherman Food, Drug, and Cosmetic Law.

We have to consider then, what does not constitute the dispensing of a new drug under the provisions of the applicable state law. We turn to the definition of the terms "drug" and "new drug" as they are used in these state and federal acts. The statutory definitions of the term "new drug" are controlling, regardless of any other meaning attributed to the word "new" or the phrase "new drug" in common parlance or in other authority. (See United States v. Articles of Drug Labeled "Quick-O-Ver" (D.Mo. 1967) 274 F.Supp. 443, 445, fn. 2 citing 61 Cases of Jam v. United States (1950) 340 U.S. 593 and Western Union v. Lenroot (1944) 323 U.S. 490.)

A drug within the meaning of section 26670 is defined, generally, by reference to its actual or intended use. Section 26010 provides that:

"'Drug' means any of the following:

"(a) Any article which is recognized in an official compendium.

"(b) Any article which is used or intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or any other animal.

"(c) Any article other than food, which is used or intended to affect the structure or any function of the body of man or any other animal.

"(d) Any article which is used or intended for use as a component of any article designated in subdivision (a), (b), or (c) of this section.

"The term 'drug' does not include any device."

(See also Bus. & Prof. Code § 4031.)

A new drug is defined by section 26021 in two different ways. 2/ First, it means a drug the composition of which is such that it 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 or advertising thereof. Secondly, even if it has become so recognized as safe and effective for use under such conditions, it is a new drug if it has not been used to a material extent or for a material time under such conditions as are prescribed, recommended, or suggested in the labeling or advertising thereof. (See Cal.Admin. Code, tit. 17, § 10360.)

It is clear then that a drug is determined to be a new drug by reference to the conditions prescribed, recommended, or suggested in the labeling or advertising of the drug, and it is a rule of statutory construction that that which is

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2. Section 26021 provides that:

"'New drug' means either of the following:

"(a) Any 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 or advertising thereof.

"(b) Any 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."

necessarily implicit in the express terms of a statute is equally a part of the statute. (Sondeno v. Union Commerce Bank (1977) 71 Cal.App.3d 391, 395.) As a necessary corollary, a drug which may be dispensed, sold, or given away without the necessity of including in the labeling the conditions or effective use for which the drug is prescribed, recommended or suggested is not a new drug within the meaning of section 26021. From this analysis it may be concluded logically that a pharmacist does not dispense, sell or give away a new drug pursuant to a physician's prescription if the labeling requirements to which a pharmacist must comply do not require a statement of the prescribed, recommended or suggested use of the drug to accompany a prescription drug.

Hence, it must be determined whether the labeling requirements set forth within the Health and Safety Code require a pharmacist to place a reference as to the effective use of the drug on the label or the written material supplied with a drug filled by prescription or, stated in the alternative, whether a pharmacist's failure to include such statements referring to the drug's effectiveness constitutes an act of misbranding for which the pharmacist is subject to prosecution. This determination is necessary since the absence of a labeling requirement specifying the effective use of a prescription drug will operate to remove prescription drugs from the class of drugs denominated as new drugs within the meaning of section 26021. This conclusion is manifest from the corollary interpretation of section 26021, that is, a drug which may be sold in the absence of a labeling requirement specifying the effective use of the drug is not a new drug within the meaning of the Sherman Food, Drug and Cosmetic Law.

We turn then to the relevant misbranding sections for purposes of identifying those labeling requirements in the context here germane for which noncompliance will subject a pharmacist to prosecution. Section 26651 provides that: "[i]t

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3. Unless otherwise stated the term "physician" in this opinion includes physician, dentist, podiatrist or veterinarian, licensed in accordance with the laws of the State of California.

is unlawful for any person to misbrand any drug or device." 4/

Section 26636 sets forth that:

"Any drug subject to Section 26660 [prescription drugs] is misbranded unless the manufacturer, packer, or distributor of the drug includes, in all advertisements and other descriptive matter issued or caused to be issued by the manufacturer, packer, or distributor with respect to that drug, a true statement of all of the following:

" . . . . . .

"(d) Such other information, in brief summary relating to side effects, contraindications, and effectiveness as shall be required by regulations promulgated by the department.

"Regulations relating to side effects, contraindications, and effectiveness issued pursuant to Section 502(n) of the federal act (21 U.S.C. Sec. 352(n)) are the regulations establishing information requirements relating to side effects, contraindications and effectiveness in this state. The department may, by regulation, make other requirements relating to side effects, contraindications, and effectiveness whether or not in accordance with the regulations adopted under the federal act." (Emphasis added.)

Section 26019 defines "manufacture" as follows:

"'Manufacture' means the preparation, compounding, propagation, processing, or fabrication of any food, drug, device, or cosmetic. The term 'manufacture' includes repackaging or otherwise changing the container, wrapper, or labeling of any food, drug, device, or cosmetic in furtherance of the distribution of the food, drug, device, or cosmetic. The term 'manufacture' does

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4. Section 26661 states that:

"The act of selling a drug or device contrary to the provisions of Section 26660 shall be deemed to be an act which results in the drug or device being misbranded while held for sale."

not include repackaging from a bulk container by a retailer at the time of sale to its ultimate consumer."

Since a pharmacist compounds drugs, it may be assumed (without deciding) that in certain contexts a pharmacist is a manufacturer within the meaning of section 26019 and is subject to the misbranding provision of section 26636. In summary, under this analysis and the above-mentioned assumption, a pharmacist qua manufacturer is guilty of misbranding if he or she sells a new drug or if he or she fails to include a statement of the drug's effective use in the labeling or printed material accompanying any drug. (§§ 26670 and 26636 respectively.)

These two sections when read in this context seemingly place a pharmacist in an untenable position. If a physician requests that a prescription be filled for what would be deemed a new drug, a pharmacist is subject to prosecution under section 26636 if he or she fails to include with the drug a statement of the drug's effective use. On the other hand, by inclusion of the statement of effective use a pharmacist may be subject to prosecution under section 26670 since by virtue of the statement the drug may be deemed to be an unapproved new drug, i.e., a new drug which has not received an effective application pursuant to 21 U.S.C.A. § 355, subdivision (b), or from the State Department of Health. In short, does a pharmacist face these alternatives: (1) he may commit an act of misbranding by failing to state the effective use of a drug upon its label (section 26636) or (2) he may dispense a new drug in violation of section 26670 by stating what constitutes an effective use of a drug where the drug has not been approved as to that use by the appropriate state and/or federal authorities.

As will be discussed below, a pharmacist is not subject to the twin horns of this dilemma if drugs are compounded for a patient pursuant to a prescription of a licensed physician.

Since a pharmacist qua manufacturer, under our assumption, would be subject to prosecution 5/ for misbranding

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5. Section 26801 sets forth that:

"Any person who violates any provision of this division or any regulation adopted pursuant to this division is guilty of a misdemeanor and shall, if convicted, be subject to imprisonment for not more than six months in the county jail or a fine of not more than one thousand dollars ($1,000), or both such imprisonment and fine. If the violation is committed after a previous conviction under this section which has become final, or if the violation is committed with intent to defraud or mislead, the person shall be subject to imprisonment for not more than one year in the county jail or a fine of not more than one thousand dollars ($1,000), or both such imprisonment and fine."

if he or she sells a new drug that has not received the appropriate federal or state approvals, the question remains whether a drug ordered by a physician by prescription is a new drug within the meaning of that term as it is used in the state act. The conclusion is that it is not.

As discussed before, a new drug obtains the status of a new drug by its being referenced to the conditions prescribed, recommended, or suggested in the labeling or advertising of the drug. Relevant to this interpretation is section 26662 which exempts prescription drugs from numerous labeling requirements. As pertinent here, section 26662 expressly exempts prescription drugs from the labeling requirements of section 26636, which as discussed above, requires information regarding the side effects, contraindications and effective use of the drug to be placed on the labeling. In addition, the labeling provisions of section 26638 6/ are exempted, which among other

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6. Section 26638 provides that:

"Any drug or device is misbranded unless its labeling bears all of the following information:

"(a) Adequate directions for use.

"(b) Such adequate warnings against use in pathological conditions or by children where its use may be dangerous to health.

"(c) Adequate warning against unsafe dosage or methods or duration of administration or application.

"Warnings shall be in such manner and form as are necessary for the protection of users.

"If the department determines that any requirement of subdivision (a), as applied to any drug or device, is not necessary for the protection of the public health, the department may adopt regulations exempting such drug or device from these requirements.

"Any drug or device exempted under Section 502(f) of the federal act (21 U.S.C., Sec. 352(f)) is exempt from the requirement of this section. The department, however, may adopt any regulation including a drug or device within, or excluding a drug or device from the requirements of this section, whether or not the inclusion or exclusion of such drug or device is in accord with the federal act."

things, require adequate directions for use (§ 26638 subd. (a)). Adequate directions for use have been interpreted under title 17, California Administration Code, section 10405 subd. (a) (1), to include when necessary "[s]tatements of all conditions purposes or uses for which such drug . . . is intended, . . ."

While section 26662 exempts prescription drugs from the labeling requirements of section 26638, that section requires, as a condition of exemption, that certain statements appear on the label. As pertinent here, subdivision (b) of section 26662 requires a statement of "the directions for use of the drug." While section 26662 does not further amplify upon the meaning of the phrase "directions for use," it is evident from the statutory predecessor of section 26662 that the Legislature intended the pharmacist to include those instructions as contained in the physician's prescription. Thus section 26252 provided in both its 1951 (Stats. 1951, ch. 1615, § 6) and 1955 version (Stats. 1955, ch. 1079, § 7) preceding its repeal and replacement as section 26662 7/ that the label include those directions for use "as prescribed by such member of the medical, dental or veterinary profession." In addition, it is evident from the interpretation given to section 26662 under Title 17, section 10415 of the California Administrative Code that the phrase "directions for use" was intended to refer to the instructions contained within a prescription. In this regard title 17, California Administrative Code, section 10415 provides as follows:

> "A drug subject to the requirements of Section 26252 [26662] of the code, shall be exempt from Section 26244 [26638] 8/ if all the following conditions are met:

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7. Section 26252 repealed by Statutes 1970, chapter 1573, section 3, and replaced by section 26662 as added by Statutes 1970, chapter 1573, section 5, and repealed by Statutes 1971, chapter 646, section 25. The present section 26662, similar to the former section 26662 was added by Statutes 1971, chapter 646, section 28 and amended by Statutes 1977, chapter 479, section 4. (See § 26051).

8. Former section 26244, added by Statutes 1939, chapter 730, § 1, effective January 1, 1940, amended by Statutes 1959, chapter 966, § 2 and repealed by Statutes 1970, chapter 1573, section 3, was replaced by the present 26638, added by Statutes 1970, chapter 1573, section 5. (See § 26051.)

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". . . . . .

"(2) The label of the drug bears:

"(A) The statement 'Caution: Federal Law prohibits dispensing without prescription,' or 'Caution: Not to be dispensed without a prescription'; and

"(B) The recommended or usual dosage; and

"(C) The route of administration, if it is not for oral use; and

". . . . . ." (Emphasis added.)

Therefore, a pharmacist who complies with the labeling provisions of section 26662 is not required to include a statement of the drug's effective use on the prescription label. As a consequence, a prescription drug which otherwise may be considered a new drug if sold commerically without a prescription by a drug manufacturer, is not a new drug within the meaning of section 26021, subdivisions (a) and (b) when dispensed by a pharmacist because the required statutory reference to the prescribed, recommended or suggested conditions for effective use of the drug (a necessary prerequisite for there to be a new drug) is absent.

From this analysis it may be seen that the Legislature intended the new drug provisions to afford protection to consumers from drugs put into the market place by drug manufacturers without the judgment of experts independent of the manufacturer. This same danger is deemed not to arise in situations where a drug is compounded by a pharmacist pursuant to a licensed practioner's prescription. A pharmacist is not acting so as to create a market for the drug. He is implementing the decision of a physician who has exercised independent judgment as to the safety and effectiveness of a particular drug in the treatment of a patient.

This is not to say that a pharmacist can not engage in regulated activities similar to those of a drug manufacturer, but rather that the compounding of drugs pursuant to a prescription is an activity distinct from that of a drug manufacturer and that the pharmacist while engaged in this conduct is not subject to the new drug provisions. (See also Bus. & Prof. Code § 4034.)

Having concluded that the Sherman Food, Drug, and Cosmetic Law does not prohibit the activities addressed by questions one and two, we must determine whether a similar conclusion is warranted under the pertinent provisions of the Federal Food, Drug, and Cosmetic Act. We note that there are substantial questions raised regarding the reach of the regulatory provisions of the Federal Act with respect to the activities in question. (See United States v. Sullivan (1948) 322 U.S. 689; F.T.C. v. Simeon Management Corporation (N.D.Cal. 1975) 391 F.Supp. 697, affirmed (1976) 532 F.2d 708; United States v. Dianovin Pharmaceuticals, Inc. (1st Cir. 1973) 475 F.2d 100, cert. den. (1973) 414 U.S. 830; United States v. 39 Cases, More or Less, etc. (E.D.Mich., S.D. 1961) 192 F.Supp. 51.)

However, for the purpose of discussion we will assume that a pharmacist under the factual situation presented would be subject to prosecution 9/ for misbranding a drug while

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9. Penalties for violation of title 21, United States Code, section 331 are set forth in 21 United States Code section 333, which provides in part:

> "(a) Any person who violates a provision of section 331 of this title shall be imprisoned for not more than one year or fined not more than $1,000, or both.
>
> "(b) Notwithstanding the provisions of subsection (a) of this section, if any person commits such a violation after a conviction of him under this section has become final, or commits such a violation with the intent to defraud or mislead, such person shall be imprisoned for not more than three years or fined not more that $10,000, or both."

held for sale after shipment in interstate commerce 10/ if the misbranding provision of 21 U.S.C.A. section 352, subdivision (n)(3) 11/ which provides that a prescription drug is misbranded unless there is included a statement of effectiveness on the

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10. 21 U.S.C.A. § 331 provides, in part, that:

The following acts and the causing thereof are prohibited:

". . . . . .

"(k) The alternation, mutilation, destruction, obliteration or removal of the whole or any part of the labeling of, or the doing of any other act with respect to, a food, drug, device, or cosmetic, if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded."

11. 21 U.S.C.A. § 352, provides in part that:

"A drug or device shall be deemed misbranded

". . . . . .

"(n) In the case of any prescription drug distributed or offered for sale in any State, unless the manufacturer, packer, or distributor thereof includes in all advertisements and other descriptive printed matter issued or caused to be issued by the manufacturer, packer, or distributor with respect to that drug a true statement of (1). . ., (2). . ., (3) such other information in brief summary relating to side effects, contraindications, and effectiveness as shall be required in regulations which shall be issued by the Secretary in accordance with the procedure specified in section 371(e) of this title: . . ."

printed materials accompanying a drug, applies to pharmacists when dispensing prescription drugs. Furthermore, if 21 U.S.C.A. section 352, subdivision (n) (3) is interpreted to require addition of a statement of effectiveness by pharmacists when dispensing prescription drugs, a pharmacist could be subject to prosecution for a violation of section 26670 of the state law (no person shall sell, dispense or otherwise give away new drugs) if the required statement of effective use makes the drug, as to that use, a new drug within the meaning of 21 U.S.C.A. section 321, subdivision (p), subparts (1) and (2), and thus a use for which an effective application is required under 21 U.S.C.A. section 355, subdivision (b).

New drugs are defined in 21 U.S.C.A. section 321, subdivision (p) 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."

Upon a comparison of the definition of new drug contained in 21 U.S.C.A. section 321, subdivision (p), and that contained in Health and Safety Code section 26021, we note that there is no significant difference (see discussion supra). Therefore, just as under the Sherman Food, Drug, and Cosmetic Law, a drug's status as a new drug under the Federal Act is established by its being referenced to the effective use that is prescribed, recommended or suggested in the labeling or advertising thereof. Since a statement of effectiveness may make a drug a new drug as to that use within the meaning of 21 U.S.C.A. section 321, subdivision (p), we must again revert to the labeling exemption provisions to determine whether a pharmacist must comply with the provision requiring a statement of effective use to avoid being subject to prosecution. (21 U.S.C.A. § 352, subd. (n).)

Under 21 U.S.C.A section 353, subdivision (b)(2), drugs dispensed pursuant to a prescription are exempt from the "effective use" labeling requirements of 21 U.S.C.A. section 331 when dispensed by prescription of a licensed practitioner. 12/ In addition, by the express terms of 21 U.S.C.A. section 353 subdivision (b)(2) the only statements which a pharmacist must include on the label with regard to the directions for use are those contained in the prescription itself. Since a physician need not include within a prescription either the conditions or effective use for which a drug is prescribed, it is clear for the reasons set forth above that a drug dispensed pursuant to a prescription, which does not contain a statement of the drug's effective use is not a new drug within the meaning of 21 U.S.C.A. section 321, subdivision (p), subparts (1) and (2), nor is it a misbranded drug for which a pharmacist may be prosecuted under 21 U.S.C.A. section 331.

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12. Section 353 subdivision (b)(2) states:

"(2) Any drug dispensed by filling or refilling a written or oral prescription of a practitioner licensed by law to administer such drug shall be exempt from the requirements of section 352 of this title, except subsections (a), (i) and (3), (k), and (l) of said section, and the packaging requirements of subsections (g), (h), and (p) of said

Hence, it must be concluded under both the state law and the federal act that a pharmacist does not dispense what would otherwise be considered a new drug if commercially sold without a prescription, since the labeling provisions do not require a statement of the conditions or effective use for which the drug is sold -- a necessary concomitant 13/ for there to be a new drug within the meaning of the acts being discussed.

This analysis demonstrates the validity of the conclusion as to the first question presented. However, the pharmacist does not exist, in this context, independently of the physician who issues the prescription. When we examine the provisions of the state and federal food, drug, and cosmetic acts in the context of the functions of a physician who writes the prescription intending that it be filled by a pharmacist for the benefit of the physician's patient, we are

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12. (Cont'd)

> section, if the drug bears a label containing the name and address of the dispenser, the serial number and date of the prescription or of its filling, the name of the prescriber, and, if stated in the prescription, the name of the patient, and the directions for use and cautionary statements, if any, contained in such prescription. This exemption shall not apply to any drug dispensed in the course of the conduct of a business of dispensing drugs pursuant to diagnosis by mail, or to a drug dispensed in violation of paragraph (1) of this subsection." (Emphasis added.)

13. It is clear that the Legislature or Congress could require pharmacies to provide buyers or prescription drugs with information about their effects, including side effects. If such information included representations as to the effective use of prescription drugs, language should be added which would make clear whether such a change was intended either to limit or to proscribe the existing privilege of pharmacies to dispense new drugs pursuant to a valid prescription.

compelled to the same conclusion. Additionally, consideration of this issue is necessary in order to answer the third question presented.

The purpose of the Federal Food, Drug and Cosmetic Act viewed in its broadest sense is to protect the uninformed consumer. (See United States v. Dotterweich (1943) 320 U.S. 277; United United States v. Urbuteit (1948) 335 U.S. 355; Kordel v. United States (1948) 335 U.S. 345; United States v. Naremco, Inc. (8th Cir. 1977) 553 F.2d 1138; United States v. Article . . . Consisting of 216 Carton. Bot. (2nd Cir. 1969) 409 F.2d 734; United States v. Diapulse Manufacturing Corporation (D.Conn. 1967) 269 F.Supp. 162 affd. (1968) 389 F.2d 612; United States v. 250 Jars, etc. of U.S. Fancy Pure Honey (ED.Mich.S.D. 1963) 218 F.Supp. 208 affd. (1965) 344 F.2d 288.) The protection afforded by the Federal Act, to the extent relevant, is with respect to two types of drugs purchased by the consumer: prescription and nonprescription drugs.

In purchasing nonprescription drugs, the consumer must rely upon representations of drug manufacturers as to the safety and effective use of a particular drug. Congress recognized that this reliance may have been misplaced where a drug manufacturer's enthusiasm for a new drug preceded the drug's general recognition by a body of expert opinion as being safe and effective for the stated use. In order to protect the uninformed consumer from the dangers inherent in this possibility, Congress enacted the Federal Food, Drug and Cosmetic Act to require drug manufacturers to obtain the concurrence of independent experts regarding a new drug's safety and effectiveness for treatment of a stated condition before that drug could be made available to consumers.

In a sense the act does not attempt to educate the consumer as to the efficacy of any particular drug, as contrasted to another drug, so as to change him from an uninformed consumer to an informed consumer. (See United States v. Sullivan (1948) 332 U.S. 689; Herman v. Smith, Kline and French Laboratories (ED.Wisc. 1968) 286 F.Supp. 694, United States v. Various Articles of Drugs (S.D.N.Y. 1962) 207 F.Supp. 480; United States v. Grayce, Inc. (N.D.Ind. 1954) 126 F.Supp. 6; United States v. El-O-Pathic Pharmacy (9th Cir. 1951) 192 F.2d 62.) The assumption appears to be that a danger to the consumer arises as a result of one's having to choose whether to use a drug without the knowledge to evaluate its safety or effectiveness. Therefore, the thrust of the act is to protect the uninformed consumer by eliminating from the market place those drugs supplied by drug manufacturers which have not been evaluated by experts (independent of the manufacturer) as being, in their informed judgment, safe and effective for use by such consumers.

With respect to prescription drugs, Congress recognized

that the informed judgment of a licensed practitioner was interposed between the drug manufacturer and the ultimate consumer. However, this interposition of judgment on the part of a licensed practitioner was not reflected in a less stringent regulatory scheme for the approval of new prescription drugs developed for distribution by drug manufacturers. The necessity of protecting the uninformed consumer in this instance is reflected in the fact that licensed practitioners, to a certain extent, rely upon the statements of effective drug use issued by drug manufacturers. To the extent licensed practitioners rely upon these statements, so in turn does the ultimate consumer when advised through the intermediary practitioner that a certain drug should be effective in treating a specific condition. Hence, where a drug manufacturer represents that a drug is effective for treatment of a stated condition the consumer is equally in need of protection whether the drug be a prescription or nonprescription drug. (See United States v. 10 Cartons, etc. (W.D.Pa. 1957) 152 F.Supp. 300.)

A different situation is involved, however, where a licensed practitioner in an exercise of his or her independent judgment decides to prescribe a drug for a use which, as to that use, would make the drug a new drug. In this case, neither the practitioner nor the patient, through the practitioner, is relying upon representations of the drug manufacturer as to the drug's effective use. Furthermore, the practitioner in prescribing a drug for a given condition is not promoting a drug in the commerical setting in which a drug manufacturer operates. In summary, those economic factors which gave rise to a need for federal regulation to protect the uninformed consumer are absent since the practitioner is not engaged in creating a market demand for the drug.

This view of the purpose of the act is supported by comments and reports made at the time of the adoption of the Federal Act by Congress.

Senator Royal Copeland, when introducing Senate Bill No. 2800 on the subject, stated that the Bill was drafted so as to make "certain that the medical practitioner shall not be interfered with in his practice." (78 Cong. Rec. 2728 (1934).) It is clear from the remarks of Senator Copeland at the time of introducing Senate Bill No. 2800 that the bill and its predecessors were aimed at the advertising, food, drug, and cosmetic industries. Senate Bill No. 2800 was reintroduced as Senate Bill No. 5 in the 74th Congress in 1935. Both Senate Bill No. 2800 and Senate Bill No. 5 said that the term "drug" was defined therein "for the purposes of this act and not to regulate the practice of medicine." (Emphasis added.) The House Committee on Interstate and Foreign Commerce in considering Senate Bill No. 5 omitted the latter clause because the words were thought to be unnecessary and might create confusion.

The committee further stated that the bill "does not undertake to regulate the practice of the healing arts." (H.R.Rep. No. 2755, 74th Cong., 2d sess. (1936).) Senate Bill No. 5 was not enacted in the 74th Congress and was reintroduced in the 75th Congress, again as Senate Bill No. 5 (81 Cong. Rec. 65 (1937). Not until this version of Senate Bill No. 5 reached the House were the "new drug" provisions added by the House Committee on Interstate and Foreign Commerce as section 505, subdivision (a) of the act. In explaining the "new drug" provisions, the Committee stated that the section was intended "to prevent incompetent or irresponsible manufacturers from causing wholesale deaths, rather than to penalize them after the deaths have occurred." (Emphasis added.) (H.R.Rep. No. 2139, 75th Cong., 3d Sess. (1938).)

The above view of the purpose of the Federal Act is supported by an examination of its administration. The construction given to a statute by the officials charged with its administration is entitled to great weight, especially where it is long continued and is acquiesced in by persons having an interest in the matter. (Cal. M. Express v. St. Bd. of Equalization (1955) 133 Cal.App.2d 237, 240.)

The major objective of the drug provisions of the Federal Act, as interpreted by the Food and Drug Administration, is to insure that drugs will be safe and effective for use under the conditions prescribed, recommended, or suggested in their labeling. (FDA Drug Bulletin, October 1972.) Accordingly, the pattern of federal enforcement of the new drug section of the Federal Act has been directed at the manufacturers, processors, and packers of misbranded articles who have responsibility for insuring the veracity of labeling. Indeed, the position of the Federal Food and Drug Administration is that "[I]n accordance with congressional understanding [they] have been cautious in applying the powers of the Federal Food, Drug and Cosmetic Act to interfere directly with the practice of dentistry, medicine or pharmacy." 14/ The FDA Drug Bulletin of October 1972 contains the following statement reflecting the position of the agency:

> "Congress did not intend the Food and Drug Administration to interfere with medical practice. Congress recognized a patient's right to seek

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14. Statement of J. Crout, M.D., Director, Bureau of Drugs, Food and Drug Administration, Public Health Service, Department of Health, Education and Welfare, before the House (of Representatives) Subcommittee on Intergovernmental Relations and Human Resources, Committee on Government Operations on October 31, 1975.

civil damages in the courts if there should be evidence of malpractice, and declined to provide any legislative restrictions upon the medical profession."

The determination that the use of a drug is appropriate in the treatment of the condition of one's patient is peculiarly within the competency of the physician treating the patient. That judgment by the physician was not intended to be regulated by Congress when it enacted the Federal Food, Drug and Cosmetic Act, as evidenced by the foregoing discussion and the comments and reports made at the time of the adoption of the Federal Act by Congress.

Additionally, it does not follow from the fact of a lack of general recognition among experts that a drug is safe and effective that one may infer that a particular use of a drug is either unsafe or ineffective. Neither should it follow that merely because a substance is deemed a new drug, that a physician may not lawfully prescribe differing dosages of drugs or vary the conditions of use from those recommended on a drug's label or package insert based upon their professional knowledge and judgment that such a use in the treatment of a patient is justified by scientific rationale or by medical evidence.

One federal District Court has arrived at a similar conclusion. In F.T.C. v. Simeon Management Corporation, supra, 391 F.Supp. 697, 706-707, affd. 532 F2d 708 (1976), that court stated:

"Furthermore, the FDA does not have jurisdiction to regulate the administration of a drug by a physician. In order to invoke the jurisdiction of the FDA, 21 U.S.C. § 355(a), requires a person to:

'* * * introduce or deliver * * * into interstate commerce any new drug * * *.'

"Even assuming arguendo that HCG is a new drug under the definition of new drug (21 U.S.C. § 321(p)), the California physician in his private treatment of a California patient with HCG is engaging in a manifestly different quantitative and qualitative act than introducing or delivering for introduction into interstate commerce. The FDA interpretation of the 1938 Act and its 1962 Amendments does not treat the use of HCG by a treating and prescribing physician as being in interstate commerce. The FDA has stated:

"'If an approved new drug is shipped in interstate commerce with the approved package inserts, and neither the shipper nor the recipient intend that it be used for an unapproved purpose, the requirements of section 505 of the Act are satisfied. Once the 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.' 37 Fed. Reg. 16503 (1972)."

If we were to reach a contrary conclusion a most unrealistic result would ensue. To apply section 26670 to the healing arts practitioner would mean that every time a patient was being treated with what may be technically a new drug, the treating practitioner would have to comply with the new drug provisions of the Health and Safety Code. These sections create mechanisms which simply do not fit the reality of the clinical situation. For example, they speak of new drug applications seeking approval of a new drug; (§ 26670); of six-month waiting periods on applications (§ 26671); of hearings (§ 26671); of submitting reports of investigation and testing (§ 26672); of proposed labeling and advertisement (§ 26672); of manufacturing methods facilities and controls (§ 26672); of maintaining clinical records pending approval (§ 26674); and of department orders withdrawing approval of applications (§ 26675). Patently these provisions cannot be impressed upon the local healing arts practitioner treating an individual patient without creating havoc in California clinical practice. These provisions are designed, as is their federal model, to apply to commercial activities. 15/ Applied to those ventures they make sense, applied to the clinical situation they do not.

Section 26666 provides that a practitioner may personally furnish his own patients with such drugs as are necessary in the treatment of the condition for which he attends such patient. This section appears to underscore the right of the practitioner to exercise his professional discretion when providing drugs in a therapeutic setting. The fact that section 26666 makes no distinction between new drugs and other drugs but merely refers to drugs which are

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15. The phrase "commercial activities" is assumed here to include activities of a physician or pharmacist who engages in the manufacture of drugs, i.e., other than on a person-to-person, clinical-treatment-prescription basis.

"necessary in the treatment of the condition," further indicates the inapplicability of the concept of new drug to the clinical practitioner. (See also Bus. & Prof. Code § 4051.) Even if the restrictions on new drugs were construed to apply to the practitioner, section 26666 would exclude such practitioner because it provides that he may furnish his patients with drugs and the term "drug" as defined in section 26010 necessarily includes any new drug. 16/

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16. California Administrative Code, title 17, section 10416, provides as follows:

> "Section 26666 of the Health and Safety Code shall be construed only as applying the same exemptions to labeling requirements for drugs dispensed by a physician, dentist, podiatrist, or veterinarian, as are provided for drugs sold by filling or refilling a written or oral prescription of such practitioner and shall not provide any exemption from the requirements of Section 26670 (new drugs) of the Health and Safety Code or from the requirements of Chapter 7 (commencing with Section 1700) of Division 2 of the Health and Safety Code (Cancer Law)."

The interpretation of a statute or of a regulation is a question of law. While an administrative agency's interpretation of a statute or of its own regulation obviously deserves great weight, the ultimate resolution of such legal questions rests with the courts. (Culligan Water Conditioning v. State Bd. of Equalization (1976) 17 Cal.3d 86, 93; Carmona v. Division of Industrial Safety (1975) 13 Cal.3d 303, 310.) The legal question is whether section 10416 of title 17, California Administrative Code, properly interprets the provisions of Health and Safety Code section 26666.

However, "administrative regulations that violate acts of the Legislature are void and no protestations that they are merely an exercise of administrative discretion can sanctify them. They must conform to the legislative will if we are to preserve an orderly system of government." (Morris v. Williams (1967) 67 Cal.2d 733, 737.) Administrative regulations that alter or amend the statute or enlarge or impair its scope are void and courts not only may, but it is their obligation to strike down such regulations. (Morris v. Williams supra, at 748.) There is no reason to exclude unapproved new devices from the provisions of section 26670 as is done by section 26680 while making unapproved new drugs subject to its proscriptions where the common factor is the use of such materials by practitioners within the scope

To conclude to the contrary would necessarily limit the practice of physicians in the treatment of patients to only those dosages and conditions of use of drugs which have proceeded through the expensive and time-consuming process specified as a condition of the obtaining of approval of a new drug.

Since a physician, dentist, podiatrist, or veterinarian may furnish his own patient with such drugs, including new drugs, as are necessary in the treatment of the condition for which he attends such patient, it must follow that he may write an order prescribing such drugs, including new drugs, to be dispensed by a licensed pharmacist.

If a physician, in the exercise of his professional judgment, may prescribe a particular drug for use in treating a patient, which use is not generally recognized by qualified experts as safe and effective for that use, 17/ can it be said that the licensed pharmacist, who has no personal knowledge of the condition of the patient, is required in every instance to determine whether that particular use of a drug for a particular patient constitutes an unapproved use, and, based upon his judgment that such is so, to refuse to fill the prescription in order that he may comply with section 26670? We believe more apt language is required in the relevant statutes to justify that conclusion than we find exists at this time.

Of course, the practice of pharmacy has been declared by the Legislature to be a profession. (Bus.& Prof. Code § 4046.) We do not imply that a licensed pharmacist,

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16. Cont'd

of their license privilege. In fact, a contrary conclusion is compelled by the statutory scheme. At the least such a vital and far-reaching legislative effect should not be inferred from ambiguous statutory language. If the Legislature wishes to impose such restrictions, as it is clear that they may do, they should do so by appropriate language which is not readily susceptible to either interpretation.

Accordingly, section 10416, title 17, California Administrative Code, alters and impairs the scope of Health and Safety Code section 26666 to the extent it purports to limit the practice of medicine in a manner and to an extent which is contrary to the legislative intent expressed in the Sherman Food, Drug, and Cosmetic Law. The provision of section 10416, title 17, California Administrative Code, relating to the furnishing of new drugs within the meaning of section 26670, is unforceable and void.

17. But see Cobbs v. Grant (1972) 8 Cal.3d 229, 242-244; Toole v. Richardson-Merrell, Inc. (1967) 251 Cal.App.2d 689, 704.

as an expert with respect to drugs, has no obligation, under appropriate circumstances, to consult with and advise the prescribing physician. Nor do we imply that the prescribing of a new drug or the dispensing of a new drug may not constitute negligence. We conclude only that the provisions of section 26670 do not operate to prevent a licensed pharmacist from dispensing a new drug pursuant to a bona fide prescription of a physician, dentist, podiatrist, or veterinarian for treatment of an individual patient. Nothing stated herein should be construed to imply that a licensed pharmacist must or should dispense a new drug if in the exercise of his professional judgment he believes that he should not do so, or he chooses not to do so.

The conclusions stated in answer to the first question are equally applicable to the second question. The distinction between the two questions is only that the second refers to a specific "new drug" (see Federal Food and Drug Administration Press Release dated November 26, 1975) which, we understand, has been determined to be so because of the lack of general recognition by qualified experts of its safety and effectiveness, no new drug application having been approved by the United States or the State of California for its use in root canal or endodontic therapy.

Based upon our analysis of the broader first question, it is concluded that neither section 26670 nor federal law, 21 U.S.C.A., 331, subdivision (k), prohibits a pharmacist from compounding and dispensing 18/ N-2 or RC-23 substances 19/ pursuant to a bona fide prescription order of a dentist, if the substance N-2 or RC-23 is determined by the dentist to be appropriate in the treatment of the condition for which he attends a patient, and if the component elements of such materials in any combination or singly have not been banned by state and federal law or regulation. 20/ However, strict compliance by the pharmacist with the provisions of Health and Safety Code sections 26027, 26660, and 26662 and Business and Professions

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18. See Business and Professions Code section 4049.

19. We understand that N-2 or RC-23 is a zinc oxide-eugenol-paraformaldehyde combination containing in compound, paraformaldehyde (trioxymethylene), an organic antiseptic Mercury compound (phenylmercuric borate), eugenol (p methoxy-allyl-benzene) to form a paste, as well as lead oxide, zinc oxide, hydrocortizone, prednisolene, titanium oxide or titanium dioxide, bismuth subcarbonate, busmuth subnitrate, lead tetroxide, and barium sulfate, with percentages varying according to formula.

20. The transcript of the hearings before a subcommittee of the Committee on Government Operations, House of Representatives, 94th Congress, First Session, dated October 31, 1975, establishes that there exists a nationwide controversy within the dental profession concerning the use

Code section 4036, 4047.5 and 4049 is mandatory.

Based upon the foregoing analysis it is further concluded that the Sherman Food, Drug, and Cosmetic Law does not prohibit a physician from prescribing or administering a drug for a condition not specified in the drug's advertising which has been approved subsequent to the submission of an appropriate federal or state new drug application.

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20. Cont'd.

of N-2 or RC-2B type substances for use for root canal or endodontic therapy. Howard Martin D.M.D., F.A.C.D. Georgetown University School of Dentistry, Dudley Glick, D.M.D., F.A.C.D., F.I.C.D., University of Southern California School of Dentistry, Stephen Cohen, D.D.S., University of the Pacific, testified, as we read the transcript, to the effect that there was scientific evidence available which demonstrated that "N2 and associated formulations" were not safe when used for root canal or endodontic therapy. See, for example, the testimony of Dr. Martin at page 8 of that transcript:

> "N2 has a severe derangement effect on cells. The cells cannot multiply thereby decreasing their regenerative and repair ability. Lead, mercury and titanium dioxide prevent cell multiplication while paraformaldehyde causes cellular degeneration. As N2 resorbs into tissue, its cytoxicity remains since its toxic components are water soluble. The paste, in the set state, continues to cause degeneration of cells affecting cellular respiration and leads to chronic inflammation inhibiting growth and repair.
>
> "N2 has an overall long lasting inflammatory action. The paste is resorbable, it does not form a hard tissue and it affects the periapical tissue in a deleterious manner. It leads to ankylosis, resorption, necrosis and poor clinical results. It is an irritating material which places an additional burden on the defense mechanism of the periapical tissue. The type of healing generated is questionable since there is little or no hard tissue formation and the fixed cells may eventually break down into a foci of necrotizing material. The scleretic zone has been identified as necrotic and as such is irritating to the tissue apical to the zone causing metaplastic change.
>
> "Bony reactions have been sequestration, long standing chronic inflammation, ankylosis and necrosis.

The final issue is whether a physician's representations concerning the effectiveness of a drug in treating a particular disease of the patient constitute a violation of section 26463 of the Health and Safety Code.

Section 26463 provides that it is unlawful for any person to advertise any drug or device to have any effect on thirty-seven enumerated conditions. Section 26002 provides that the term "advertisement" includes any representations which are made for the purpose of inducing, or which are

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20. Cont'd.

There is reduced healing with a concurrent production of osteoclasia and resorption. Macrophages with the paste in its granules have been found, after prolonged periods of time. This indicated the materials constant resorbability and eventually leads to defective obturation. Defective obturation is the prime cause of endontic failure.

"Lead has been demonstrated to be a bone seeker and toxic. It has been shown that lead resorbed from the root canal paste is present in increased amounts in blood, adrenals, kidney, spleen, and bone. The lead, detected, achieves the permissible daily intake from the paste filling alone. The possibility of an increased toxicological burden on the body must be considered. The duration and nature of exposure to such material must make the prudent practitioner consider alternatives especially in the light of safer and more predictable means being available.

"Paraformaldehyde is an effective antiseptic only in high concentrations. As used in pastes, the antiseptic effect is available for approximately seven to ten days. In the set state, its effect is negligible. The essence of paraformaldehyde is to create an intra-vitam fixation of tissue. This necrotizing action creates a zone of degenerated material that is a constant source of chronic inflammation and potential breakdown. As a fixing agent, the periodontal structures will also be affected creating ankylosis and resorption. The action is not self limiting and creates damage periodontally and also potentially from a restorative aspect.

"This zone has been shown histologically to be necrotic in all cases. As such, it must be regarding [sic] as a focus of constant irritation and source of breakdown. Apical to the sclerotic zone, the tissue

likely to induct, directly or indirectly, the purchase or use of any drug or device. 21/

Neither section 26002 nor section 26463 can be interpreted to apply to representations made by a physician to a patient in a clinical situation. (See F.T.C. v. Simeon Management Corporation, supra, 391 F.Supp. 697.) Informed consent on the part of the patient is necessary before medical treatment can be begun (see Cobbs v. Grant, supra, 8 Cal.3d 229, 242-244) and any medical treatment given without informed consent exposes the physician to an action in negligence. (Id. at pp. 240-241, and cases cited at pp. 239-240 therein.) Thus, the clinical situation demands that a patient be informed of all aspects of his medical situation, including diagnosis and proposed modes of treatment. This in turn requires that the patient be appraised of the medicines which will be prescribed for his condition and their use and effect, both beneficial and harmful.

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20. Cont'd.

> undergoes metaplasia. The characteristics are chronic inflammation, resorption, foreign body reactions, resorbed N2 particles, ankylosis and necrosis. As a barrier to N2 reactions, the sclerotic zone is totally ineffective and is by itself destructive to tissue."

Ramon Werts, D.D.S., Executive Director, American Endodontic Society testifed, as we understand it, that "our simplified method and the materials employed in it are safe and effective." Dr. Werts' position appears to be that any harm which has resulted from the use of N-2 was due to employing an improper technique and such harm was not inherent in the N-2 material itself.

21. Health and Safety Code section 26002 states as follows:

> "'Advertisement' means any representations, including, but not limited to, statements upon the products, its packages, cartons, and any other container, disseminated in any manner or by any means, for the purpose of inducing, or which is likely to induce, directly or indirectly, the purchase or use of any food, drug, device, or cosmetic."

This section has been interpreted to include oral representations within the concept of advertising. (People v. Galway (1953) 120 Cal.App.2d 45, 49; People v. Schmitt (1957) 155 Cal.App.2d 87, 101-102.)

Another consideration is that section 26463 prescribes representing any drug as having an effect on such conditions as diabetes, high blood pressure, and heart disease. Such conditions are commonly encountered in patients by the practicing physician and some form of treatment is required. It is not logical to conclude that the Legislature intended to prevent the practitioner from discussing with his patients the effects of drugs prescribed to treat those diseases. It is well established that the consequences of a particular interpretation of a statute are relevant in determining legislative intent (see Estate of Ryan (1943) 21 Cal.2d 498, 513). Where a statute is susceptible of two constructions, the interpretation which leads to the more reasonable result will be followed. (See Committee on the Rights of the Disabled v. Swoap (1975) 48 Cal.App.3d 505, 510. See also cases cited at p. hereinabove.)

Other provisions concerning advertising in the Sherman Food, Drug, and Cosmetic Law reflect an intent to regulate advertising in the commercial and not in the clinical sphere. Section 26464 provides an exemption from section 26463 if the advertisement is disseminated to health professionals or for public health education by persons who are not commercially interested, directly or indirectly, in the sale of such drugs or devices. 22/ Since the physician is deemed to be skilled in evaluating the efficiency of such drugs or devices and he is not motivated by profit realized from their sale, the risk posed by commercial advertising is not present so as to make these sections applicable. It is thus reasonable to assume that a physician's representations to a patient are not covered by section 26463. Further, section 26465 provides that whenever the department determines that any type of self-medication is safe and effective for any of the conditions named in section 26463, the department shall

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22. Health and Safety Code section 26464 states as follows:

> "An advertisement which is not unlawful under Section 26460 is not unlawful under Section 26463 if it is disseminated only to members of the medical, dental, pharmaceutical, or veterinary professions, or appears only in the scientific periodicals of these professions, or is disseminated only for the purpose of public health education by persons not commercially interested, directly or indirectly, in the sale of such drugs or devices."

authorize the advertisement of such drug or device. 23/ This provision confirms that the primary concern addressed by section 26463 is the purchase of an unsafe or ineffective drug or device directly by the consumer for his self-use.

Accordingly, it is concluded that section 26463 does not apply to a physician who makes representations while providing a drug or device to his patient for the conditions listed in that section.

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23. Health and Safety Code section 26465 states as follows:

> "Whenever the department determines that an advance in medical science has made any type of self-medication safe and effective as to any of the conditions, disorders, or diseases named in Section 26463, the department shall, by regulation, authorize the advertisement of any such drug or device as having a curative or therapeutic effect for such disease, subject to such conditions and restrictions as the department may consider necessary to the interests of public health."

HFN-120 Tolu-54
10B-19 GG-54

MAY 18 1984

Note To: Assistant Secretary for Health

Through: PHS-ES _____

From: Acting Commissioner of Food and Drugs

Subject: Response to DEA Concerning Control of MDMA

I have attached a draft reply to Mr. Mullen (DEA) for your signature, and FDA's scientific and medical evaluation of the substance, 3,4-methylenedioxymethamphetamine (MDMA). FDA recommends that MDMA be placed in Schedule I of the Controlled Substances Act, because MDMA has a significant potential for abuse.

DEA has asked that this evaluation be expedited because no enforcement action can be taken against producers of this drug until it is placed under CSA control.

Mark Novitch

Mark Novitch, M.D.

000281

GG-55

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date May 21, 1984

From Yng-shiuh Sheu, Ph.D.
Office of the Director, NIDA

Subject DEA Recommendation to Control 3,4-Methylene-dioxy-methyl-amphetamine (MDMA) in Schedule I of the Controlled Substances Act (CSA)

To Edward Tocus, Ph.D.
Chief, DAS, FDA

NIDA appreciates your sharing the DEA request to schedule MDMA in Schedule I of the CSA.

The direct evidence that MDMA has any abuse potential in animals is not substantiated, based on the data DEA provided. MDMA has no current medical use; however, its abuse consequences have appeared in both emergency room and medical examiners' reports of the Drug Abuse Warning Network; in the discovery of two clandestine laboratories; and having been detected in treatment programs.

NIDA does not have any objection to placing MDMA under Schedule I of the CSA.

cc:

James D. Lawrence, Deputy Director, NIDA
John Scanlon, Ph.D., Acting Director, ARC
Donald Jasinski, M.D., Scientific Director, ARC
Charles Gorodetsky, M.D., Ph.D., Scientific Director, ARC
Marvin Snyder, Ph.D., Director, DPR
Barry Brown, Ph.D., Director, DCR
James R. Cooper, M.D., Assistant Director for Medical Affairs
Nathan Kight, OD

000282

GG-57

Department of Health and Human Services
Public Health Service
Food and Drug Administration

Memorandum

Date: OCT 25 1985

To: Charlotte Johnson
Drug Enforcement Administration

From: Chief
Drug Abuse Staff
Division of Neuropharmacological Drug Products (HFN-120)

Subject: Schedule I Substances for Use in Psychotherapy

As directed, I have searched our computerized files on applications for Schedule I substances for use in psychotherapy during the last 5 years. There has been only one such application which was for the use of LSD. It was approved and the study is in progress.

Edward C. Tocus

Edward C. Tocus, Ph.D.

000283

MAR 1 3 1984

Dr. Edward Brandt
Assistant Secretary for Health
Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Dr. Brandt:

In accordance with the provisions of 21 U.S.C. 811, the Drug Enforcement Administration (DEA) has gathered and reviewed the relevant data concerning the substance, 3,4-methylenedioxymethamphetamine (MDMA). Based on this information, DEA recommends that MDMA be placed into Schedule I of the Controlled Substances Act (CSA). As further required by 21 U.S.C. 811(b), DEA is requesting that you provide a scientific and medical evaluation of the enclosed information and a scheduling recommendation for MDMA.

Briefly, our review shows that: (1) MDMA is an analog of 3,4-methylenedioxy-amphetamine, a Schedule I substance, (2) it has no legitimate medical use, (3) pharmacologically it produces stimulant and psychotomimetic effects similar to those produced by MDA but at slightly higher doses, (4) MDMA is clandestinely produced by synthetic routes analogous to those used for MDA; DEA has seized 3 laboratories capable of producing kilogram quantities of MDMA, (5) MDMA is found in the illicit drug traffic throughout the United States as evidenced by forensic laboratory submissions, and (6) it is associated with medical emergencies and at least one overdose death as reported by DAWN.

DEA has recently received requests from state officials in California and Virginia requesting that MDMA be placed under the Controlled Substances Act. Further, DEA investigations of clandestine laboratories suspected of producing MDMA are terminated once the noncontrolled status of MDMA is ascertained by enforcement personnel. No enforcement action against the producers of MDMA can be taken until it is placed under CSA control.

Docket No. 84-48

Government's Exhibit No. B-1

Date

000284

Dr. Edward Brandt

Appropriate members of the DEA staff are available to assist the Department of Health and Human Services in any way possible. In order to facilitate the exchange of information, the DEA staff is authorized to transmit relevant material directly to designated members of your staff. Mr. Gene R. Haislip, Deputy Assistant Administrator, Office of Diversion Control, will act as liaison for this exchange of information.

Sincerely,

Francis M. Mullen, Jr.

Francis M. Mullen, Jr.
Administrator

Enclosure

Schedule I Control Recommendation Under the CSA for 3,4-Methylenedioxymethamphetamine (MDMA)

Prepared by
Drug Control Section
Office of Diversion Control
January, 1984

CORRECTED VERSION

Introduction

The Drug Enforcement Administration (DEA) recommends control of 3,4-methylenedioxymethamphetamine (MDMA), a clandestinely manufactured substance encountered in the illicit drug traffic and a drug of abuse. MDMA is an N-methyl analog of 3,4-methylenedioxyamphetamine (MDA), a Schedule I substance under the Controlled Substances Act (CSA). There have been an increasing number of reports of clandestine chemists synthesizing MDMA instead of MDA in an effort to circumvent the law. MDMA has been reported in drug evidence submissions to both DEA and state/local forensic laboratories since 1970 and recently with increasing frequency. The Drug Abuse Warning Network (DAWN) reports emergency room and medical examiner episodes of MDMA. Intelligence data indicates that MDMA is sold on college campuses as "Ectasy", "XTC" or MDA.

This paper will describe the available scientific information concerning MDMA and the existing evidence of its abuse and involvement in the illicit drug traffic. The information therein supports a recommendation for control in Schedule I of the CSA.

Summary

3,4-Methylenedioxymethamphetamine (MDMA, MDM) is the N-methyl analog of 3,4-methylenedioxyamphetamine (MDA). MDMA has no current medical use and is not scheduled under the CSA. MDA is in Schedule I of the CSA. There are no known legitimate manufacturers of MDMA or MDA in the United States.

MDMA was first encountered in the illicit drug traffic and analyzed by DEA laboratories in 1970. Since that time it has been encountered 34 times by DEA laboratories (Attachment 1), reported by forensic laboratories in 8 states (Attachment 2) and reported by Pharm Chem Laboratory (Attachment 3) routinely since 1976. DEA has evidence of a number of laboratories producing MDMA for sale and use as a drug in attempts to circumvent the CSA (Attachment 4). The synthesis of MDMA is analogous to that of MDA, requires no elaborate apparatus or sophiscated techniques and can be made from readily available materials. The Drug Abuse Warning Network has reported emergency room episodes involving MDMA since 1977 and one medical examiner mention in 1979. (Attachment 5)

MDMA and MDA exhibit qualitatively similar pharmacological profiles in mice, dogs and monkeys (Hardman et al, 1973; Braun et al, 1980). Studies examining signs relating to motor, autonomic and central nervous system function in the dog and monkey showed that mescaline, MDA and MDMA gave the same qualitative responses. (Hardman et al, 1973). In mice, MDA and MDMA produced comparable analgesia and central nervous system stimulation (Braun et al, 1980). Both MDA and MDMA produce responses in dogs equivalent to those of mescaline (Hardman et al, 1973). The toxicity of MDMA, as determined by LD50's in mice (ip), rats (ip), guinea pigs (ip), dogs (iv) and monkeys (iv), is similar to although somewhat less than that of MDA (Hardman et al, 1973).

In humans both MDA and MDMA produce similar psychopharmacological effects including altered consciousness, increase in acoustic, visual and tactile sensory perceptions and mild intoxication (Shulgin et al, 1976; Anderson et al, 1978; Braun et al, 1980). The effective dose of MDMA is 100-160 mg compared to 60-120 mg for that of MDA (Braun et al 1980).

Recommendation

Based on a review of the scientific and abuse data available to DEA concerning MDMA, DEA recommends that MDMA be placed into Schedule I of the Controlled Substances Act. The necessary criteria for placing a substance in Schedule I, as set forth in section 202(b)(1) of the CSA are as follows:

1) The drug or other substance has a high potential for abuse;

2) The drug or other substance has no currently accepted medical use in treatment in the United States; and

3) There is a lack of accepted safety for use of the drug or other substance under medical supervision.

The term "potential for abuse" is defined in House Report No. 91-1444 to include any or all of the following four elements (House Report 1970):

a) Evidence that individuals are taking the drugs in amounts that create a hazard to their health or the safety of the community.

The DAWN system has reported emergency room episodes resulting from the use of MDMA as well as 1 death attributed to MDMA use. (Attachment 5)

b) Diversion from legitimate channels

Since there is no legitimate medical use nor manufacturer of MDMA, there can be no diversion. The MDMA encountered by law enforcement personnel and submitted to forensic laboratories is produced in clandestine laboratories. (Attachment 4)

c) Self-administration of the drug without medical supervision.

Submissions of MDMA to forensic laboratories is indicative of street trafficking and therefore non-medical use of MDMA. MDMA has been identified in submissions to DEA, non-federal and private drug analysis laboratories since 1970 in all parts of the United States. (Attachments 1,2,3) DAWN ER and ME reports are also indicative of unsupervised use of MDMA. (Attachment 5)

d) Evidence that the drug in question is so related in its action to another drug or drugs that it's likely that it will have the same potential for abuse

MDMA is the N-methyl analog of MDA, a substance in Schedule I of the CSA. Both substances exhibit similar pharmacological profiles in mice, dogs and monkeys. (Hardman et al, 1973; Braun et al, 1980) Human studies also indicate that MDA and MDMA produce qualitatively similar responses, differing in the effective dose. (Shulgin et al, 1976; Anderson et al, 1978; Braun et al, 1980) On the street MDMA is often sold as MDA. MDMA is controlled in Schedule H of the Canadian Food and Drugs Act along with MDA, LSD and other psychotomimetic substances. (Bailey, 1979)

but see 4

An examination of the above elements describing abuse potential lead one to conclude that MDMA has an abuse potential similar to that of MDA. MDA, in Schedule I, and MDMA, have high potentials for abuse, satisfying criteria (1) for Schedule I.

MDMA has no known legitimate medical use for treatment in the United States thus satisfying criteria (2) for Schedule I.

MDMA has no accepted legitimate medical use; it is found in the illicit drug traffic; it is of clandestine origin; and it has been associated with medical emergencies. All these facts satisfy criteria (3) for Schedule I.

The necessary criteria for Schedule I as outlined in Section 202(b)(1) of the CSA (21 U.S.C. 812(b)(1)) are satisfied. Therefore, the DEA recommends to the Secretary of the Department of Health and Human Services that 3,4-methylenedioxymethamphetamine (MDMA) be placed into Schedule I of the CSA.

Following are the considerations of the factors listed in 21 U.S.C. 811(c) relevant to placing MDMA under CSA control:

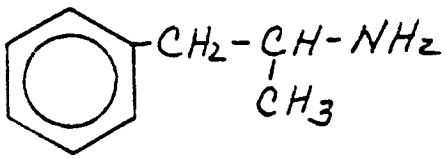
1) Its actual or relative potential for abuse

MDA and MDMA are ring substituted derivatives of phenethylamine. Amphetamine and methamphetamine are prototype phenethylamine derivatives. At therapeutic doses amphetamine is a sympathomimetic stimulant and leads to psychotomimetic activity only at high doses. A methylenedioxy group on the aromatic nucleus leads to compounds, such as MDA, with psychotomimetic and stimulant activity. (Braun et al, 1980). N-Methylation of amphetamine yields methamphetamine which produces similar effects to those of amphetamine. Similarly N-methylation of MDA yields MDMA which retains psychotomimetic and stimulant activity (Nichols et al, 1981). Other ring substituted phenethylamines include 3,4,5-trimethoxyamphetamine (TMA), 4-methyl-2,5-dimethoxyamphetamine (STP), 4-bromo-2,5-dimethoxyamphetamine (DOB), para-methoxyamphetamine (PMA) and 3-methoxy-4,5-methylenedioxyamphetamine (MMDA) (See figure 1). With the exception of MDMA, all are in Schedule I of the CSA.

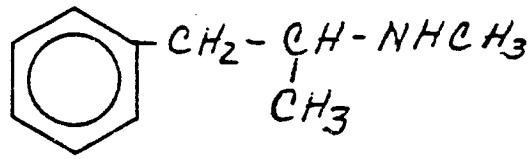
One method of demonstrating abuse potential is showing pharmacological equivalence to another substance with a known abuse potential. In this case MDMA can be compared to MDA, its desmethyl analog and a substance with a known high potential for abuse.

Braun, Shulgin and Braun tested MDA and MDMA in mice using stretch, hot-plate and tail-flick tests in analgesic screening procedures. These tests showed that both MDA and MDMA had substantial analgesic activity at the doses tested. In each case the analgesic effect of MDMA were greater than those of MDA. Braun, Shulgin and Braun also studied MDA and MDMA in mice for increased motor activity using activity cages through which 10 light beams shone; the number of interruptions in the light beams caused by the movement of the animals was measured. (Braun et al, 1980). MDMA produced approximately three times as much activity as MDA in the first three hours after administration.

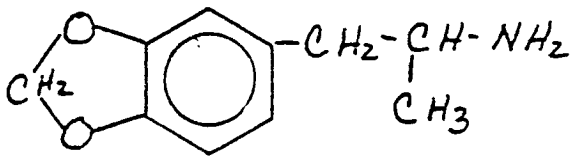
Hardman, Haavik and Seevers observed the presence or absence of 15 signs related to motor, autonomic and central nervous system function in the unanesthesized dog and monkey after intravenous administration of mescaline, MDA and MDMA (Hardman et al, 1973). Their observations are set forth in Table 1.



Amphetamine



Methamphetamine



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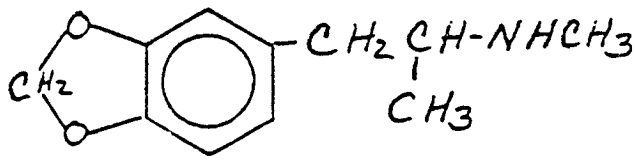
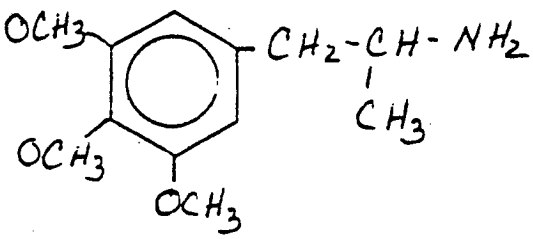
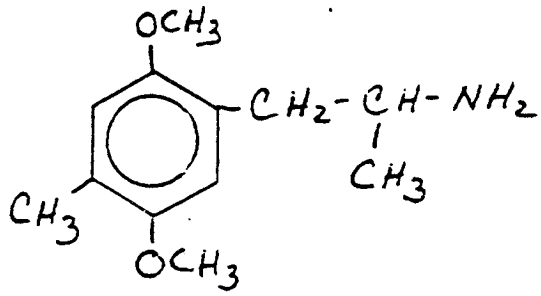


MDMA



TMA



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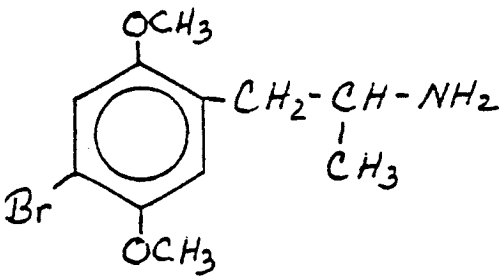
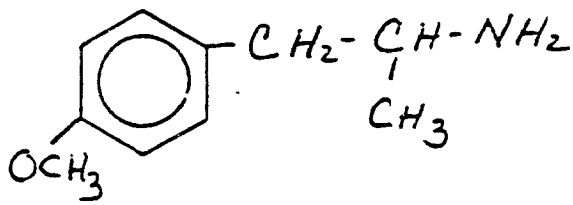
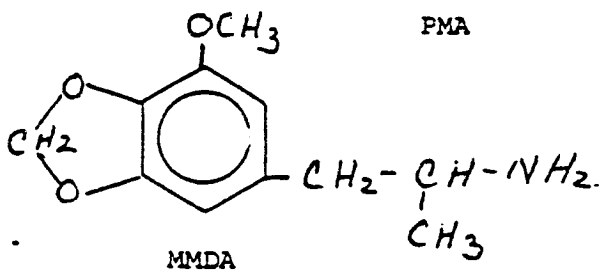


DOB



PMA



MMDA

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Figure 1

Table 1

Observation	Mescaline	MDA	MDMA
Motor Activity			
Ataxia	D,M	D	D,M
Convulsions (clonic)	D,M	D,M	D
Convulsions (tonic)	D,M	D,M	D,M
Musclar rigidity	D,M	D,M	D,M
Muscle tremors	D,M	D,M	D,M
Autonomic Activity			
Mydriasis	D,M	D,M	D,M
Piloerection	M	D,M	D
Salivation	D,M	D,M	D,M
Vascular flushing	D,M	-	-
CNS Activity			
Emesis	D	D	D
Apprehension/Fright	D,M	D,M	D,M
Bizarre Body Attitudes	D	D	D
Hallucinations (apparent)	D	D,M	D,M
Dyspnea	D,M	D	M
Hyperpnea	D,M	D	D,M

Doses

Substance:	Dog (D)	Monkey (M)
Mescaline	5-60 mg/kg (N=22)	10-200 mg/kg (N=17)
MDA	0.5-15 mg/kg (N=27)	1-20 mg/kg (N=21)
MDMA	5-50 mg/kg (N=28)	10-75 mg/kg (N=28)

With the exception of vascular flushing, all signs related to motor, autonomic and CNS function were observed in either species for mescaline, MDA and MDMA. The symptoms are all part of the pharmacologic response to intravenous mescaline in the dog.

Griffiths, Brady and Bradford evaluated 17 phenethylamines and psychomotor stimulants using substitution procedures for determining whether these drugs will maintain self-administration in baboons (Griffiths et al, 1976). MDA maintained levels of self-administration above saline at doses of 1.0 mg/kg. Phentermine, diethylpropion, phenmetrazine, phendimetrazine and benzphetamine all maintained self-administration at similar doses. Although MDMA was not tested, its pharmacological similarity to MDA in mice, dogs and monkeys suggest that it would also maintain self-administration in baboons.

Shulgin and Nichols first reported the psychotomimetic properties of MDMA in man (Shulgin et al, 1976). No description of the testing methods, subjects or procedures were given. Nevertheless, MDMA produced effects comparable to those of marihuana, psilocybin, or to lower levels of MDA. MDMA was reported to have a higher threshold level than MDA but otherwise to be very similar in potency. The MDMA effective dosage range was 75-150 mg orally with effects noted one-half hour after administration and lasting approximately 3 hours. A sympathomimetic stimulation lasted for several additional hours.

Further studies by Shulgin and co-workers on the effects of MDMA on normal human subjects focused on its optical isomers (Anderson, 1978). The procedure used was one reported by Shulgin et al in 1969 (Shulgin, 1969). The effective dose for the racemate was verified to be between 75 and 160 mg. Using 35 clinical trials, Shulgin described the intoxication resulting from MDMA as ++ using a scale of -, ±, +, ++ and +++ at the effective doses. Mydriasis and jaw clenching were frequently noted physical symptoms.

Braun et al determined the psychotomimetic properties of MDA and MDMA using 5 normal volunteers, 35-55 years old (Braun et al, 1980). The authors reported that MDA had greater activity although MDMA was almost equally effective. The psychopharmacological profiles of MDA and MDMA were very similar. The effects noted included a drive-increasing effect, change in consciousness without hallucinations, increase in acoustic, visual and tactile sensory perceptions, decrease in tension and mood-lightening. Physical symptoms noted included mydrasis and pulse acceleration. In a few cases anxiety that showed itself psychosomatically as nausea was noted. (Shulgin, 1979)

MDMA has been identified in 34 submissions of drug evidence to DEA laboratories since 1970 (Attachment 1). These exhibits were from 12 states and included seizures from 3 clandestine laboratories (Attachment 4). Additionally, 12 reports from forensic laboratories in 8 states have verified encounters of MDMA since 1978 (Attachment 2). Pharm Chem Laboratories, through their Analysis Anonymous program, has consistently reported submissions of MDMA in each year since 1976 (Attachment 3). MDMA was placed into Schedule H of the Canadian Food and Drugs Act effective June 11, 1976 after its appearance in illicit drug traffic and after the seizure of a clandestine laboratory in Ontario. (Bailey, 1979).

The DAWN system has reported 8 emergency room episodes involving MDMA between 1977 and 1981 (Attachment 5). Four reports stated that MDMA was taken alone. Psychic effect and dependence were the motivational factors for taking the drug in 4 cases. One DAWN Medical Examiner episode of MDMA (alone) has been reported from Seattle, Washington. At least one drug treatment program has

has reported patients who have used MDMA (Fishbein, 1983). Because of the similarity in effects between MDA and MDMA and because MDMA is sometimes sold as MDA it is possible that some abuse episodes attributed to MDA are actually due to MDMA use.

MDMA, based on its pharmacological similarity to MDA and reports of actual abuse has an abuse potential similar to that of MDA and commensurate with Schedule I control under the CSA.

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

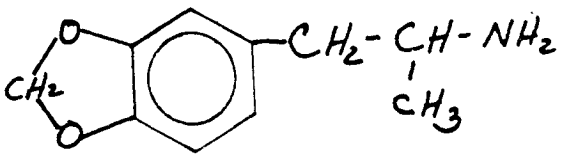
MDMA has been shown to have a pharmacological profile similar to that of MDA in mice, dogs, monkeys and man. (Hardman, 1973; Braun, 1980)

An evaluation of the two optically active isomers each of MDA and MDMA and their racemic forms was made in rabbits using evoked rectal hyperthermia as a measure of central activity (Anderson et al, 1978). The results of these tests showed that racemic MDMA is slightly less potent than MDA. Further, the "S" isomer of MDMA is more effective than the "R" isomer as a CNS agent while for MDA the "R" isomer is the more effective one. This relationship between the optical isomers of MDMA and those of MDA was also shown in a study of normal human subjects (Anderson et al, 1978). The "S" isomer of MDMA was more active than the "R" isomer giving a rating of ++ at doses of 80-120 mg (Scale = -, +, +, ++, +++ for levels of intoxication). The effective dose of the "R" isomer of MDMA is approximately 300 mg. This reversal of the activity of the optical isomers of MDA and MDMA suggest that MDMA does not act by demethylation to MDA. (Anderson et al, 1978).

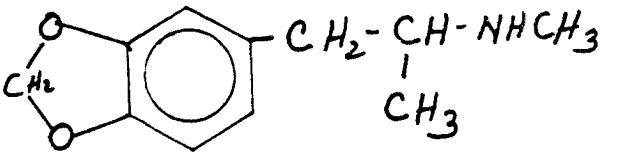
It has been suggested that the active ("R") isomer of MDA might act by a direct receptor effect while the active ("S") isomer of MDMA might work by the release of an endogenous neurotransmitter (Nichols et al, 1980). Nichols et al studied the isomers of MDA and MDMA for their effect on the release of [3H] serotonin from whole rat brain synaptosomes. No differences were noted in the potencies of the MDA isomers while the "S" isomer of MDMA was more effective in inducing the release of the neurotransmitter than the "R" isomer. Since it is the "S" isomer of MDMA which is the active enantiomer, the activity of MDMA may be due to the release of the serotonin neurotransmitter.

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

Chemically, MDMA is 3,4-methylenedioxy-N-methyl-phenylisopropylamine. It is the N-methyl analog of MDA (See figure 2). It can exist as the hydrochloride salt with a melting point of 151-3 C.



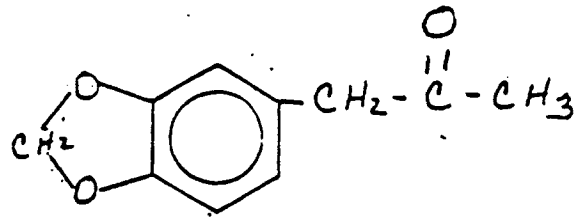
MDA



MDMA

Figure 2

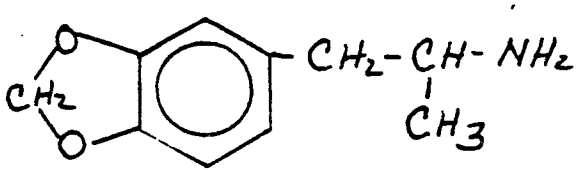
The first reported synthesis of MDMA was from safrole by converting it to its bromo derivative followed by reaction with methylamine. (Biniecki et al, 1960). Bailey et al describe the synthesis of MDMA from 3,4-methylenedioxyphenylacetone using a Leuckart reaction with N-methylformamide and hydrolysis of the N-formyl derivative (Bailey et al, 1975). A third synthesis for MDMA described in the literature starts with piperonal which is reacted with nitroethane, ammonium acetate and acetic acid to form a nitrostyrene derivative which is reduced to the ketone and then reacted with methylamine to form MDMA (Rabjohns, 1963). Using the method of Borch et al, MDMA can be synthesized by the reductive amination of the appropriate ketone in the presence of sodium cyanoborohydride (Borch et al 1971). The MDMA syntheses used in clandestine laboratories are analogous to those for MDA (See figure 3).



1-(3,4-methylenedioxyphenyl)-2-propanone

ammonia

methylamine



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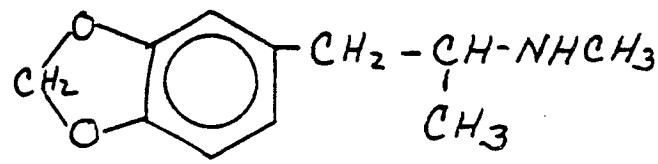
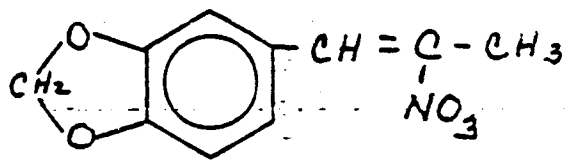


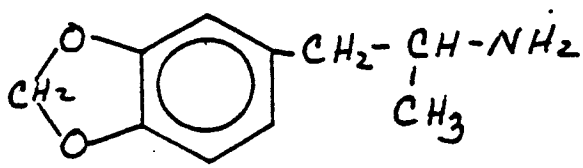
MDMA



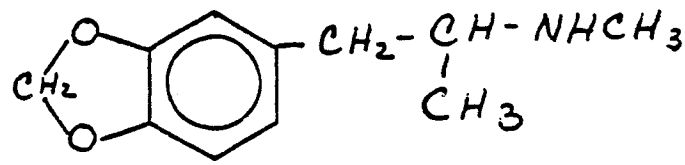
3,4-methylenedioxy-β methyl-β nitrostyrene

reduction

reduction with methylamine



MDA



MDMA

Figure 3

Both of these synthesis have been used in clandestine laboratories. They use readily available, inexpensive chemicals and apparatus and do not require the skills of a professional chemist.

4) Its history and current pattern of abuse

MDMA was first encountered by DEA laboratories in 1970 in a submission from the Chicago Police Department. Since that time DEA laboratories have analyzed 34 exhibits of MDMA from 12 states as reported in STRIDE (Attachment 1). This data indicates that MDMA is purchased or seized as MDA, Ecstasy, XTC, MDM or MDMA itself (Attachments 2,3 and 6). Whether the user is aware that he or she is purchasing MDMA and not MDA is not clear. Interrogation of clandestine laboratory operators from laboratories producing MDMA, however, show that these chemists are synthesizing MDMA to circumvent the CSA since MDMA is not controlled. DEA has seized at least 3 clandestine laboratories synthesizing MDMA, 1 in 1973, 1 in 1977 and 1 in 1983 (Attachment 4). Authorities in Canada seized a clandestine MDMA laboratory in Ontario in 1976. It had the capacity to produce several pounds of MDMA per day (Bailey, 1979).

MDMA is taken orally as evidenced by the seizures of clear gelatin capsules containing MDMA reported by forensic laboratories. The sole medical examiner mention for MDMA reported in DAWN listed the route of administration as oral. DAWN data indicates that MDMA is taken alone (4 out of 8 ER mentions and the ME mention) and its users are motivated by MDMA's psychic effects or their dependence on the substance. A number of MDMA submissions to forensic laboratories originated on college campuses thus indicating that users are probably in the young adult age group. The DAWN medical examiner mention of an MDMA caused death involved a 23 year old white male.

The current pattern of abuse, based on the above data and particularly on the fact that MDMA is sold as MDA, is similar to that of MDA.

5) The scope, duration and significance of abuse

DEA laboratories have analyzed 34 exhibits of drug evidence containing MDMA. These submissions have come from the following 12 states: California (9), Illinois (6), Washington, D.C. (3), Colorado (3), Tennessee (3), Florida (2), New York (2), Pennsylvania (2), Alabama (1), Louisiana (1), North Carolina (1) and Oregon (1). The 34 exhibits of MDMA consisted of 47,321 dosage units (calculated at 130 mg per dosage unit) with 5 of the exhibits clear capsules and the remainder powders.

Other forensic laboratories have reported at least 41 encounters with MDMA to DEA since January 1, 1978 (Attachment 2). In many cases the quantity of MDMA or its form were not included in these reports. Nevertheless these exhibits accounted for 1821.64g and at least 12 capsules with MDMA. The reports came from Oregon (10), Texas (9), Virginia (7), California (6), North Carolina (6), New York (1), Maryland (1) and Tennessee (1). Additionally Pharm Chem Laboratories, an anonymous testing laboratory for street drugs reported 27 submissions of MDMA between January 1, 1976 and December 31, 1979 Attachment 3). Between January 1, 1980 and December 31, 1982, they reported 101 submissions of MDMA or MDA (data for individual submissions were not available). Pharm Chem Laboratories has reported 4 MDMA samples through April, 1983. Additionally DEA has been receiving inquiries with increasing frequency from DEA and other law enforcement personnel concerning the control status of MDMA since it is being encountered on the illicit market.

DEA has seized 3 clandestine laboratories synthesizing MDMA (Attachment 4). The laboratories seized were believed to be making a controlled substance (MDA). Intelligence information, based on precursor purchases, indicates that there have been and are more clandestine laboratories operating. Investigations were not continued due to the noncontrolled status of MDMA.

In April, 1973, DEA seized a clandestine MDMA laboratory in Tennessee with 900g of MDMA and 12 kg of methylamine, a necessary chemical in one of the MDMA syntheses. A second laboratory was seized in 1977 near San Francisco, California. In addition to finding 150 ml and 0.03g of finished MDMA, DEA chemists found 1696g of 3,4-methylenedioxy-β-methyl-β-nitrostryene (MDMA intermediate), 412g of piperonal and 1000 ml of methylamine (both MDMA precursors). In September, 1983, DEA seized a third MDMA clandestine laboratory in Miami, Florida. Both finished product (1696g of MDMA) and immediate precursor (3535 ml of 3,4-methylenedioxyphenyl-2-propanone) were confiscated. Both STRIDE and Pharm Chem Laboratory data indicate the presence of impurities in many of the MDMA samples. These impurities are believed to be intermediates, by-products and unreacted chemicals from the synthesis of MDMA. A clandestine MDMA laboratory was also seized in Ontario in 1976. It had the capacity to produce pound quantities of MDMA daily (Bailey, 1979).

Between January 1, 1977 and April 1, 1981, there were 8 DAWN emergency room mentions involving MDMA (Attachment 3). Six (6) of the mentions were from San Francisco, California and 1 each from Illinois and Massachusetts. Since MDMA users frequently believe they are using MDA, it is likely that the DAWN MDA emergency room mentions contain some cases of MDMA use. The lone DAWN medical examiner mention for MDMA occurred in Seattle, Washington in July, 1979. MDMA was taken alone by the oral route of administration.

The scope of MDMA abuse is nationwide with reports of illicit trafficking occurring consistently since 1970. Clandestine synthesis of MDMA has been documented by the seizures of laboratories since 1973. Use of MDMA has resulted in medical emergencies and 1 death as shown by DAWN.

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

MDMA exhibits a similar pharmacological profile to that of MDA in animals and humans (Braun et al, 1980). Therefore, the risk to the individual and to the public from the abuse of MDMA is similar to the risks associated with MDA use. Since 1972 MDA has been reported in 344 DAWN emergency room mentions and 22 examiner reports; MDMA has been reported in 8 DAWN emergency room and 1 medical examiner mention. Law enforcement investigation reports indicate that MDMA use is associated with intoxicated and paranoid behavior (Hudson, 1983; Fishbein, 1983; Crispino, 1981).

Hardman et al measured the toxicity of a number of phenethylamines, including mescaline, MDA and MDMA, in mice (ip), guinea pigs (ip), dogs (iv) and monkeys (iv) (Hardman et al, 1973). Drugs were administered as single injections of the hydrochloride salt in saline. LD50's were calculated on the basis of death within 24 hours after drug administration and expressed as mg/kg or mmol/kg. A motor toxicity ratio (LD50 in mmol/kg of mescaline/LD50 in mmol/kg of MDA or MDMA) was calculated with mescaline given the value of 1.0 (See table 2).

Table 2

	Rt. of Admin.	N	LD50 (mg/kg)	LD50 (mmol/kg)	Molar tox ratio
Mescaline					
mouse	i p	40	212(202-222)	0.86(0.82-0.90)	1.0
rat	i p	28	132(108-161)	0.53(0.44-0.65)	1.0
guinea pig	i p	32	328(289-373)	1.33(1.17-1.51)	1.0
dog	i v	16	54 (46-64)	0.22(0.18-0.26)	1.0
monkey	i v	17	130(105-161)	0.53(0.42-0.65)	1.0
MDA					
mouse	i p	92	68(50-92)	0.32(0.23-0.43)	2.68
rat	i p	24	27(19-40)	0.13(0.09-0.19)	4.07
guinea pig	i p	60	28(23-45)	0.13(0.07-0.21)	10.02
dog	i v	17	7(5-10)	0.03(0.02-0.005)	7.34
monkey	i v	18	6(5-9)	0.03(0.02-0.04)	17.65
MDMA					
mouse	i p	50	97(89-106)	0.42(0.39-0.46)	2.04
rat	i p	32	49(46-52)	0.21(0.20-0.23)	2.52
guinea pig	i p	16	98(88-111)	0.43(0.38-0.48)	3.09
dog	i p	16	14(8-23)	0.06(0.03-0.10)	3.67
monkey	i p	26	22(17-28)	0.09(0.07-0.12)	5.89

Thus, animal toxicity data indicate that MDMA is between 2 and 6 times more toxic than mescaline and between 1.5 and 3 times less toxic than MDA. Although the toxic dose of MDA in man is not known there have been reports of MDA associated deaths in both the United States and Canada. Based on the relative toxicities of MDA and MDMA in animals (MDA = 1.5 to 3.0 x MDMA) and the effective doses of MDA (60-120 mg) and MDMA (100-160 mg) in humans it is likely that MDMA and MDA are associated with similar toxic reactions.

Since there are no legitimate commercial producers of MDMA, clandestine chemists may not take the necessary time, care or precautions to ensure a pure final product. DEA laboratories and Pharm Chem Laboratories have found inpurities in samples of MDMA which they analyzed. Shulgin and Jacob reported a potential misrepresentation of MDA or MDMA due to the use of 3,4-methylenedioxybenzylacetone in place of 3,4-methylenedioxyphenylacetone (Shulgin, 1982). Both of these substances have been sold as piperonylacetone, a precursor in the synthesis of MDA and MDMA. Reductive amination of 3,4-methylenedioxyphenylacetone yields either MDA if ammonia is used or MDMA if methylamine is used. However reductive amination of 3,4-methylenedioxybenzylacetone with ammonia or methylamine results in amines which are chemically similar to MDA and MDMA but pharmacologically and toxicologically destinct entities. Neither of these latter amines have been reported as being evaluated in humans.

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7) Its psychic or physiological dependence liability.

Data concerning the specific physical or psychic dependence liability of MDMA have not been reported. Griffiths et al reported that MDA maintained self-injection performance in baboons at doses of 1.0-5.0 mg/kg (Griffiths et al, 1976). A cyclic pattern of self-administration, similar to that observed with d-amphetamine, was observed to a limited extent with MDA - one anminal had a cyclic pattern at 5.0 mg/kg. In light of the close chemical and pharmacological similarity of MDMA to MDA, it is probable that MDMA would provide similar self-administration performance in baboons.

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

Not applicable.

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Attachment 1
Exhibits of Drug Evidence Submitted to
DEA Laboratories and Identified as MDMA
(STRIDE: 1-1-72 to 10-19-83)

	Date	Location	Quantity	How Acquired	Remarks
3	3-31-72	Chicago, Ill.	12.75g	P	as MDA
	"	"	37.79g	"	"
	6-1-72	Evanston, Ill.	2 caps	FS	"
3	4-25-73	Cedar Hill, Tenn.	0.093g	Lab S	filter paper
	"	"	890g	"	-
	"	"	1.08g	"	-
5	4-21-74	Champaign, Ill.	5 caps	S	Campus Security
	"	"	0.75g	"	"
	"	"	0.110g	"	"
	6-12-74	Aspen, Colo.	1 cap	S	-
	"	"	0.413g (76%)	S	-
12	11-11-75	San Rafael, Cal.	0.540g	"	+ MDA
0					
4	2-4-77	Sacramento, Cal.	150 ml	Lab S	Reaction Vessel
	"	"	0.031g (100%)	"	-
	7-11-77	Martinez, Cal.	0.210g	Unknown	-
	8-10-77	New York, N.Y.	1.730g (36%)	S	-
2	6-30-78	Redwood City, Cal.	1,813g	Unknown	-
	8-10-78	San Rafael Cal.	2,268g	Unknown	-
3	1-25-79	Eugene, Ore.	0.30g	Unknown	-
	5-31-79	Arvada, Colo.	5.10g (31.1%)	P(560)	-
	9-26-79	Washington, D.C.	0.461g (31%)	S	-
3	1-14-80	Metairie, La.	0.120g	Unknown	-
	3-13-80	Birmingham, Ala.	0.082g	Unknown	-
	10-19-80	Washington, D.C.	0.508g	Unknown	-
2	7-8-81	"	0.001g	S	scale
	10-7-81	Martinez, Calif.	2 caps	Unknown	-
4	6-21-82	San Isidro, Calif.	600 caps	S	-
	10-15-82	Los Gatos, Calif.	0.820g (100%)	FS	-
	10-29-82	Charlotte, N.C.	0.200g	"	-
	12-8-82	Long Beach, N.Y.	83.860g	S	-
4	4-25-83	Allentown, Pa.	1.0g (30.5%)	S	labeled MDA
	"	"	3.7g (31.1%)	"	"
	9-9-83	Miami, Fla.	281.2g	Lab S	flask
	"	"	668.6g	"	plastic tube

P = Purchase
S = Seizure
FS = Free Sample
Lab S - Clandestine Laboratory Seizure

Attachment 2
MDMA Reports from Non-Federal
Forensic Laboratories

1) 5-8-79: Letter from the Director, Oregon State Crime Laboratory Division stating that his laboratory system had encountered between 5 and 10 MDMA street samples in the preceeding 6 months, primarily from Eugene, Oregon.

2) 5-11-79: Letter from the Director, San Mateo County, California Laboratory stating that his laboratory had analyzed 3 MDMA exhibits, one of them containing a substantial amount.

3) 5-24-79: Letter from the Laboratory Supervisor, Tennessee Department of Safety Crime Laboratory stating that their Knoxville laboratory had received several MDMA cases during the preceeding year. All exhibits were clear capsules containing an off-white powder and purchased as either Ecstasy or MDA.

4) 6-20-79: Letter from the Supervisory Drug Chemist, Texas Department of Public Safety stating that MDMA had been identified 6 times during the preceeding 3 years.

5) 6-20-79: Letter from the Supervisory Drug Chemist, North Carolina State Bureau of of Investigation stating that in the preceeding 2 years his laboratory had identified MDMA in six submissions, all from the eastern part of the state.

6) 7-9-79: Letter from the Supervisory Drug Chemist, United States Army Criminal Investigation Laboratory stating that in October of 1978, 2 exhibits of pure MDMA were submitted from Norfolk, Virginia.

7) 11-25-81: Telephone call from the Director, Westchester County New York Forensic Laboratory who stated that his laboratory had analyzed an exhibit of MDMA which consisted of 200 mg of white powder in a clear gelatin capsule.

8) 7-14-82: Letter from a chemist in the California Department of Justice Laboratory stating that she had identified 3 MDMA exhibits as follows:

5-2-78 - 1811.5g pure MDMA from San Francisco Airport
6-5-78 - 0.5g MDMA from San Mateo County
3-31-82 - 8.3g MDMA from Santa Barbara

9) 8-20-82: Letter from a chemist at the Fort Worth Texas Criminalitics Laboratory stating that 2 MDMA exhibits were identified as follows:

4-19-82 - 0.04g brown powder in a clear capsule
8-19-82 - 0.27g white powder in a plastic bag

10) 12-28-82: Letter from the Toxicology Lab Supervisor, Texas Department of Public Safety stating that an exhibit containing 0.14g of powder was identified as MDMA in November, 1982.

11) 10-13-83: Letter from a chemist at the Northern Virginia Regional Forensic Laboratory stating that 5 MDMA exhibits had been analyzed as follows:

1-29-82 -	2	clear capsules	(Richmond, Va.)
3-82 -	2	" "	" "
5-6-82 -	2	" "	(Charlottesville, Va.)
3-3-83 -	1	" "	(Arlington, Va.)
10-12-83 -	2	" "	(Lexington, Va.)

12) 12-15-83: Letter from the Chief Chemist, Montgomery County, Maryland Crime Laboratory stating that his laboratory identified 1 MDMA exhibit containing 0.946g of white powder in 5 paper packets.

Attachment 3
Samples of MDMA Analyzed by
Pharm Chem Laboratories, Inc.
(1976-1983)

Year	Number of Submissions
1976	5
1977	3
1978	8
1979	7
1980	41 (includes MDA and MDMA)
1981 (Jan., Feb., Aug.-Dec.)	19 (includes MDA and MDMA)
1982	41 (includes MDA and MDMA)
1983 (through April)	4

Pharm Chem Laboratories through its Analysis Anonymous services provides laboratory analysis services to individuals who submit drug samples for identification. Located in Menlo Park, California, Pharm Chem Laboratories receives most of the samples from the West Coast of the United States. The samples submitted are usually obtained "on the street" and many times are not what they are alleged to be.

Attachment 4
DEA Seizures of MDMA
Clandestine Drug Laboratories

Date	Location	MDMA Seized	Precursors/ Intermediates	Capacity*
4-25-73	Cedar Hills, Tennessee	900g	12 kg methylamine	greater than 900g
2-4-77	San Francisco, California	0.03g 150 ml	412g piperonal 1000 ml methylamine 1.7 kg 3,4-methylenedioxy-ß-methyl-ß-nitrostyrene	1.7 kg
9-9-83	Miami, Florida	949g	3.5 l 3,4-methylene-dioxyphenyl-2-propanone	greater than 1 kg
4-22-82**	Atlanta, Georgia	-	500 ml methylamine 100g 3,4-methylenedioxy-phenylacetone	100g

* Based on finished product plus intermediates or precursors
** Laboratory not seized, chemicals specific for the synthesis of MDMA were ordered and delivered.

Attachment 5
MDMA DAWN DATA
Emergency Room Mentions

Total DAWN System (9-15-83)

Date	Location	Alone/In Comb.	Motivation	Source
2nd quarter, 1977	San Francisco, CA	In Comb.	Psych. eff./Dep.	Unk
4th quarter, 1977	"	" "	Unk	Unk
2nd quarter, 1978	Chicago, Ill.	" "	Suicide	Unk
"	San Francisco, CA	Alone	Psych. eff./Dep.	Street Buy
"	"	"	" "	" "
"	"	"	" "	Unk
4th quarter, 1979	"	"	Unk	Unk
1st quarter, 1981	Boston, Mass.	In Comb.	Suicide	Unk

Medical Examiner Mentions

Date	Location	Alone/In Comb.	Motivation	Source
3rd quarter, 1979	Seattle, Wash.	Alone	Psych. eff./Dep.	Unk

Age - 23
Race - White
Sex - Male
Manner of Death - Accidental/Unexpected
Cause of Death - Direct - single drug cause
Number of Drugs - 1
Support for cause of death - toxicology lab report, autopsy, physical symptoms, statement by family or friend
Administration - oral
Means of ID - Blood, urine, other fluid/tissue

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

JUN 6 1984

Mr. Francis M. Mullen, Jr.
Administrator
Drug Enforcement Administration
Department of Justice
Washington, D.C. 20537

Dear Mr. Mullen:

This is in further response to your letter of March 13 in which you requested a scientific and medical evaluation of data involving 3,4-methylenedioxymethamphetamine (MDMA), as well as recommendations for scheduling the substance. We have evaluated the data and the eight-factor analysis, according to the provisions of section 201(b) of the Controlled Substance Act (CSA). The staff of the Food and Drug Administration, following discussions with your staff, have made several minor changes to the eight-factor analysis document.

As a result of our evaluation, we believe MDMA has a high potential for abuse and presents a significant risk of harm to the public health. It is our recommendation that MDMA be placed in Schedule I of the CSA. A copy of our evaluation is enclosed.

Sincerely yours,

Acting James F. Dickson for
Edward N. Brandt, Jr., M.D.
Assistant Secretary for Health

Enclosure

Evaluation of the DEA Recommendation to Control
3,4-Methylenedioxymethamphetamine (MDMA)
in Schedule I of the CSA

The Drug Enforcement Administration (DEA) requested this evaluation in a letter to Asst. Secretary Edward Brandt, M.D. dated March 13, 1984, in accordance with 21 U.S.C. 811(b). Enclosed with the letter was a document containing the data and basis for the recommendation of DEA.

DEA recommends 3,4-methylenedioxymethamphetamine (MDMA) be controlled in Schedule I of the Controlled Substances Act (CSA).

DEA finds the reports of pharmacological activity and actual abuse are sufficient to conclude MDMA is closely related to 3,4,methylenedioxy-amphetamine (MDA) which is currently a Schedule I substance. DEA has concluded that:

1. MDMA has a high potential for abuse.

2. the substance has no currently accepted medical use in treatment in the United States; and

3. there is a lack of accepted safety for use of the drug or other substance under medical supervision.

The basis for these three findings of DEA was presented in an analysis of the eight factors specificed in 21 U.S.C. 811(c). These findings meet the criteria for placement of a drug in Schedule I.

Recommendation

DEA recommends 3,4-methylenedioxymethamphetamine be controlled in Schedule I of the CSA; DHHS concurs with this recommendation for the following reasons.

1. MDMA is chemically and pharmacologically related to the Schedule I substance MDA. This relationship is the same that amphetamine bears with methamphetamine which is a methyl group on the nitrogen of the amine. This difference is reflected in the chemical names of the substances which contain "meth" for methyl. Studies cited in the DEA document show MDA and MDMA both have analgesic activity in several procedures in mice, and both substances produced increased motor activity or stimulant activity in mice. When tested in dogs and monkeys MDMA produced a spectrum of central nervous system, autonomic nervous system and motor activity similar to that obtained with MDA and mescaline.

When tested in human volunteers, MDMA was again found to be similar to MDA. Both substances produced a change in consciousness without hallucinations, a decrease in tension, a heightening of mood, and an increase in acoustic, visual and tactile perception. They both caused increased heart rate and mydriasis.

2. MDMA can be synthesized easily using readily available materials. DEA presented several alternative pathways for the synthesis of MDMA which have been described in the scientific literature. Thus, the clandestine manufacture of MDMA in several laboratories around the country is highly likely. DEA provided information indicating four laboratories were found in four different states: Tennessee, California, Florida and Georgia. Chemicals in these clandestine laboratories indicated several synthetic methods of making MDMA were being used.

3. MDMA abuse has occurred in the past and continues to be a problem. There is no known legitimate use of MDMA in humans. Information from the STRIDE program at DEA indicates MDMA has been reported 34 times in 12 states over an eleven-year period. Such widespread distribution indicates Federal action to control the problem is appropriate. The most serious problem has been in California. In May, 1978, 1811.5g of pure MDMA was obtained at the San Francisco Airport by the California Department of Justice. In addition, 1813g were found in Redwood City on June 30, 1978 and 2268g were found in San Rafael, California on August 10, 1978 indicating the manufacture was most probably in California. Such large quantities have not been reported to DEA outside of California.

4. MDMA can produce harm to the public health. Studies in experimental animals which were included in the DEA report indicate MDMA is more toxic than mescaline and less toxic than MDA on a milligram basis. Since 1972 MDMA has received 8 DAWN mentions and one (1) medical examiner report. This rate is not significant except to indicate the existence of human use of MDMA. By comparison, MDA has received 344 DAWN mentions and 22 medical examiner reports. The difference in numbers of reports is considered to be more an indication of availability rather than degree of toxicity.

Accordingly, DHHS has concluded it is in the interest of preventing actual significant harm to the public health that MDMA should be controlled in Schedule I.

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3,4-Methylenedioxymethamphetamine (MDMA)
in Schedule I of the CSA

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Accordingly, DHHS has concluded it is in the interest of preventing actual significant harm to the public health that MDMA should be controlled in Schedule I.

Credit related life, accident, and health insurance may be written by Family Guardian Life Insurance Company, an affiliate of Citicorp Person-to-Person Financial Center of Florida, Inc. and Citicorp Homeowners, Inc.

7. *Citicorp*, New York, New York (consumer finance and credit-related insurance activities; Kansas and Missouri): To expand the activities and service area of its subsidiary, Citicorp Person-to-Person Financial Center, Inc., Overland Park, Kansas, through a *de novo* office of its subsidiary, Citicorp Homeowners, Inc., Overland Park, Kansas, to engage in activities in which Citicorp Person-to-Person Financial Center proposes to engage in making, acquiring and servicing, for its own accountant and for the account of others, of extensions of credit to individuals secured by liens on residential or non-residential real estate; and the sale of mortgage life and mortgage disability insurance directly related to extensions of mortgage loans. The proposed service area for the aforementioned proposed activities shall be comprised of the entire states of Kansas and Missouri. The proposed expanded service areas of the Citicorp Person-to-Person Financial Center, Inc. shall be the entire states of Kansas and Missouri for a portion of its previously approved activities, specifically, the making or acquiring of loans and other extensions of credit, secured or unsecured, for consumer and other purposes; the sale of credit related life and accident and health or decreasing or level (in the case of single payment loans) term life insurance by licensed agents or brokers, as required; the sale of consumer oriented financial management courses; and the servicing, for any person, of loans and other extensions of credit. The activities in which the proposed *de novo* office of Citicorp Homeowners, Inc. will engage are: the making or acquiring of loans and other extensions of credit, secured or unsecured, for consumer and other purposes; the sale of credit related life and accident and health or decreasing or level (in the case of single payment loans) term life insurance by licensed agents or brokers, as required; the sale of consumer oriented financial management courses; the the servicing, for any person, of loans and other extensions of credit; the making, acquiring and servicing, for its own account and for the account of others, of extensions of credit to individuals secured by liens on residential or non-residential real estate; and the sale of mortgage life and mortgage disability insurance directly related to extensions of mortgage loans. The proposed service area of Citicorp Homeowners, Inc. shall be comprised of the entire States of Kansas and Missouri for all the aforementioned activities. Credit related life, accident, and health insurance may be written by Family Guardian Life Insurance Company, an affiliate of

Docket No. 84-48

Government's Exhibit No. B-14

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 82N-0162]

Proposed Recommendations to the Drug Enforcement Administration Regarding the Scheduling Status of Marihuana and Its Components and Notice of a Public Hearing

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) announces (1) its proposed recommendations, including scientific and medical evaluations, on the appropriate scheduling of marihuana plant materials under the Controlled Substances Act and (2) that the proposed recommendations will be the subject of a public legislative-type hearing to be held on September 16, 1982. The proposed recommendations are published to give interested persons the opportunity to comment on the recommendations and on the scientific and medical evaluations. FDA will consider these comments as well as the information gathered from the public hearing in preparing its final recommendations and scientific and medical evaluations of the marihuana plant materials before transmitting them to the Assistant Secretary for Health, Department of Health and Human Services (DHHS). The Assistant Secretary for Health is responsible for making the DHHS recommendation to the Drug Enforcement Administration (DEA).

DATES: Comments on the proposed recommendations by October 1, 1982. Notice of participation in the public hearing by August 27, 1982. Public hearing to be held September 16, 1982.

ADDRESSES: Written comments on the proposed recommendations to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857. Written or oral notice of participation along with the text or comprehensive outline to the Division of Neuropharmacological Drug Products (HFD-120), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3800.

FOR FURTHER INFORMATION CONTACT: Edwin V. Dutra, Jr., Bureau of Drugs (HFD-30), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-6490.

SUPPLEMENTARY INFORMATION:

I. Background

The plant, *Cannabis sativa*, commonly known as marihuana, contains hundreds of chemical compounds. Sixty-one of the chemicals that have been identified in the plant—the cannabinoids—are specific to connabis. Ten are now routinely quantified in identifying cannabis samples (Ref. 1).

The major psychoactive ingredient contained in the marihuana plant is delta-9-tetrahydrocannabinol (THC). THC content in cannabis plants varies not only among the different parts of a single plant (flowers, leaves, stems, seeds, etc.), but also at different stages of development of the same part of a single plant. The geographic location in which the plant is grown and the time of day at which the plant is harvested also affect THC content.

The variability of THC content in natural plant material tends to render the marihuana plant, resin, leaves, and seeds difficult substances for precise scientific investigation, and scientific and medical evaluations have therefore focused primarily on THC itself, and its immediate synthetic precursor, cannabidiol.

Nonetheless, marihuana itself is currently under investigation in the United States as an agent useful in, among other purposes, the control of nausea and vomiting from cancer chemotherapy, in the reduction of the vision-destroying increase in intraocular pressure which occurs in open-angle glaucoma, and in the reduction of muscular spasticity in certain neurologic diseases (Ref. 1).

Cannabis, cannabis resin, cannabis extracts, and tinctures of cannabis are controlled in Schedule I of the 1961 Single Convention on Narcotic Drugs (Single Convention), to which the United

States is a party. Schedule I is the most restrictive schedule in the Single Convention with mandated regulatory controls. Schedule I also includes heroin, morphine, and cocaine. Its major controls are import/export permits, quotas, prescriptions, and prevention of drug stockpiling and accumulations. In addition, cannabis and cannabis resin are controlled concurrently in Schedule IV of the Single Convention. Schedule IV is best described as a "Super Schedule I" because it highlights the need for additional controls to be placed on certain drugs scheduled concurrently in Single Convention Schedule I. Heroin is the prototype for drugs in this schedule. The drugs in Schedule IV of the Single Convention are considered particularly dangerous and lack demonstrated therapeutic value. Although Schedule IV drugs are not subject to specific additional controls under the Single Convention, the treaty calls upon individual countries to use discretion in imposing whatever additional controls are necessary to protect the public health, including, if appropriate, a prohibition on production and trade. The Single Convention requires the United States to impose certain domestic controls on the marihuana plant materials listed above. The United States carries out these responsibilities under the Controlled Substances Act (CSA) (21 U.S.C. 801 et seq.).

In 1970 Congress enacted the CSA, establishing control schedules I through V (21 U.S.C. 812(b) (1) through (5)). Congress placed marihuana in schedule I of the CSA, the classification providing for the most stringent domestic controls. See 21 U.S.C. 812. The findings required for schedule I drugs or substances are: high potential for abuse; no currently accepted medical use in treatment in the United States; and lack of accepted safety for use under medical supervision. The major schedule I controls are: limitation of dispensing to research use only; the requirement of separate recordkeeping; and limitation of the amounts produced during a given calendar year, i.e., quotas.

The CSA contains procedures by which changes in scheduling can be effected (21 U.S.C. 811(a)) including "on petition of any interested person". In May 1972, the National Organization for the Reform of Marijuana Laws (NORML) petitioned the Bureau of Narcotics and Dangerous Drugs (now the Drug Enforcement Administration, DEA) under section 201(a) of the CSA (21 U.S.C. 811(a)) to remove marihuana and its components from control under the CSA or to move marihuana and its components to a less restrictive schedule. DEA denied NORML's requests (37 FR 18097; September 1, 1972). NORML appealed the denial to the United States Court of Appeals for the District of Columbia Circuit, and, in *NORML* v. *Ingersoll*, 497 F.2d 654 (D.C. Cir. 1974), the court ordered DEA to hold hearings and reconsider the NORML petition on the basis of evidence introduced at the hearings. Following these hearings, DEA again denied the NORML petition and ruled that the substances at issue would remain in CSA schedule I (40 FR 44164; September 25, 1975). NORML appealed the second denial and the court remanded the petition to DEA with instructions to refer it to the Secretary of DHHS for medical and scientific findings and recommendations for rescheduling. *NORML* v. *DEA*, 559 F.2d 745, 750 (D.C. Cir. 1977). The court directed the Secretary of DHHS to make evaluations and recommendations for each of the following cannabis materials: "cannabis" and "cannabis resin" (minimum control—CSA II); cannabis leaves (minimum control—CSA V); cannabis seeds capable of germination (minimum control—CSA V); synthetic tetrahydrocannabinol (THC) (no minimum control under CSA). The "minimum controls" schedules are the least restrictive domestic schedules consistent with the treaty obligations under the Single Convention on Narcotic Drugs, 1961, as interpreted by the court. THC was not listed by the court as having a minimum domestic schedule because THC is not controlled under the Single Convention. (THC is subject to control under the Psychotropic Convention, however, and thus is subject to control under the CSA.)

In addition, the court directed DEA to comply with the rulemaking procedures in 21 U.S.C. 811 (a) and (b) after it received the Secretary's evaluation and recommendation.

In June 1977, DEA referred the NORML petition to the Secretary of the Department of Health, Education, and Welfare (now DHHS). FDA's Controlled Substances Advisory Committee (CSAC) considered the NORML petition in November 1977 and March 1978. The CSAC (now the Drug Abuse Advisory Committee (DAAC)) recommended that the marihuana plant materials remain in CSA scheule I and that THC and cannabidiol be rescheduled to CSA schedule II. by letter dated June 4, 1979, the Secretary recommended that all these substances remain in schedule I. The advisory committee's rationale for recommending placing THC and cannabidiol in Schedule II was that it would facilitate research on the substances. The Secretary concluded, however, that facilitation of research was not relevant to any of the scheduling criteria established by the statute and, therefore, was not an appropriate basis for a scheduling recommendation.

In the Federal Register of June 20, 1979 (44 FR 36123), DEA denied NORML's petition and denied a request for hearing on the ground that there was lack of substantial evidence to support lesser control of the substances that are the subject of NORML's petition.

NORML petitioned the Court of Appeals for review of DEA's final order denying the petition. On October 16, 1980, the court ordered that the case be remanded to DEA and that DEA refer all the substances at issue to DHHS for scientific and medical findings and recommendations on scheduling. The court directed that the DHHS review take into acount new evidence concerning medical use of the substances at issue. *NORML* v. *DEA and HEW*, No. 79-1660 (D.C. Cir., October 16, 1980). On April 22, 1981, DEA referred the NORML petition to DHHS for review. DHHS Has adopted the following procedures in making the evaluations and scheduling recommendations for cannabis-containing substances (a separate procedure applies to THC, see 47 FR 10080, March 9, 1982):

1. Review by FDA of evidence concerning the uses of those substances, including comment from other appropriate units in DHHS.

2. Publication of the proposed scientific and medical evaluations and scheduling recommendations in this Federal Register notice for public comment.

3. The holding of a legislative-type hearing under 21 CFR Part 15 on the proposed findings and recommendations (see details below in Part IV).

4. Consideration of the comments received as a result of the Federal Register notice and consideration of the pertinent information generated by the hearing in preparing FDA's findings and recommendations for the Assistant Secretary for Health.

5. Review of the evaluations and recommendations by the Assistant Secretary for Health and transmittal to DEA.

II. Scheduling Recommendation

FDA proposes to recommend to the Assistant Secretary for Health that the marihuana plant materials that are the subject of the NORML petition remain in schedule I.

FDA notes that the ultimate determination of the scheduling status of th marihuana plant materials under the C will be influenced not only by the rer of these proceedings but also by U aty obligations under the Single C vention as interpreted by the court in *NORML* v. *DEA*. In *NORML* v. *DEA*, the court found that the Single Convention prescribes different controls fc various parts of the marihuana or cannabis plant. Thus, the court concluded that the minimum domestic controls under the CSA for those materials required by the Single C ivention were also different. 559 F.2d 735, 757 (D.C. Cir. 1977). The court, in its directive to the Secretary of DHHS to make evaluations and recommendations o the cannabis materials subject of the NORML petition, delineated the minimum domestic control schedule required by the Single Convention for e ch of the substances at issue (see above). FDA's proposed conclusions are, however, based solely on its medical a l scientific review of available data, n on its interpretation of this country's treaty obligations. FDA has carefully considered, from a medical and s entific standpoint, each of the five C A schedules as well as no control and tentatively concludes that the marihuana substances at issue meet the f s only for CSA schedule I.

Marihuana Materials To Be Considered

Under the CSA (21 U.S.C. 802(15)):

The term "marihuana" means all parts t the plant Cannabis Sativa L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin. Such term does not include the mature stalks of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination.

As previously noted, this ducument will address three separate categories of marihuana products: (1) cannabis and cannabis resin, (2) cannabis leaves, and (3) cannabis seeds capable of germination.

Cannabis is the entire plant material including the seeds, the resin, the leaves, the stems, the stalk, and all extracts obtained from the plant. Cannabis resin, which is generally referred to as hash, is a concentrated extract from the plant. The composition of the cannabis plant, and of cannabis extract, has been investigated and reported in the Journal of Natural Products (Ref. 2). This reference reports a total of 421 known chemicals with new ones constantly being discovered and reported. Among the known compounds reported are 61 cannabinoids (chemical compounds perhaps unique to cannabis). In the following discussion, cannabis and cannabis resin will be referred to in most places collectively as "cannabis".

Cannabis leaves contain the active substance THC and are the primary ingredients for making cannabis cigarettes. An analysis of the THC content of cannabis plant parts published in the Journal of Pharmaceutical Sciences (Ref. 3) showed the male flowers contained 1.8 percent THC, the bracts, or female flower, 3.7 percent, the small female leaves, 1.4 percent, leaves from the male plant, 1.0 percent, stems from the male plant, 0.89 percent THC, and seeds from the female plant, 0.01 percent. THC content varies significantly in leaves from various cannabis plants and from leaves within the same plant. The National Institute on Drug Abuse has reported results from an analysis of various samples of cannabis obtained in 1976. The THC content of leaves from five separate samples varied from 2.51 percent THC to 4.68 percent.

The third category of marihuana material that must be analyzed is cannabis seeds capable of germination. As discussed above, the seeds themselves have a very low percentage of THC content and are not known to have any potential for misuse except in being used to grow marihuana plants.

In making a scheduling recommendation, the Department must consider the eight factors listed at 21 U.S.C. 811(c). FDA's analysis of these eight factors with respect to each of the marihuana plant materials that are the subject of the NORML petition follows:

1. *Its actual or relative potential for abuse (21 U.S.C. 811(c)(1)).* The legislative history of the CSA, or Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (see House Report 91-1444, Part I (Ref. 4)), defines potential for abuse as including the following elements:

(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;

(2) There is significant diversion of the drug or drugs containing such a substance from legitimate drug channels;

(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 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, thus making it reasonable to assume that there may be significant diversions 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 to the safety of the community.

These elements will be discussed for each of the materials at issue.

a. *Cannabis and cannabis resin.* 1. FDA proposes to fin that individuals take cannabis in sufficient amounts to create a hazard to their health or to the safety of other individuals, or of the community. The extent of this use is discussed under Factors 4 and 5. The hazards to health are discussed under Factors 2, 3, and 6.

2. FDA proposes to find that there is not now a significant diversion of cannabis from legitimate drug channels. Cannabis is currently available through legitimate channels for reserach purposes only. The lack of significant diversion may result from the availability of illicit cannabis of equal or greater potency. If the illicit availability were not so widespread, there would presumably be additional pressure for diversion from legitimate channels.

3. FDA proposes to find that a significant number of persons take cannabis on their own initiative rather than on the basis of medical advice. When compared with the amount illicit cannabis available for persons to take on their own initiative, the amount of drug distributed in the course of medical research (the only currently authorized taking of cannabis under medical supervision) is insignificant. Approximately 10,000 to 15,000 times as much illicit cannabis as legitimate cannabis is available for distribution. Of the total amount of cannabis available for legitimate use, only approximately 5 to 10 percent was actually distributed for research in 1980 and the remainder remained under security in storage. It can be concluded that the overwhelming majority of individuals using cannabis do so on their own initiative, not on the basis of medical advice from a practitioner licensed to administer the

drug in the course of professional practice. An indication of the numbers of individuals taking the drug illicitly is given under Factors 4 and 5 concerning the current pattern and scope of abuse.

4. The fourth element in potential for abuse defined in the legislative history and discussed above does not apply to cannabis.

Considering the four elements discussed above, FDA proposes to conclude that because of the large amount of materials which is illicitly available and the number of individuals taking the drugs on their own initiative that cannabis and cannabis resin have a high potential for abuse.

b. *Cannabis leaves.* The four elements described above can be applied to cannabis leaves in two ways. First, cannabis leaves can be considered in the way they are now available in illicit use, i.e., in conjunction with other parts of the marihuana plant in the mixture that has been referred to above as "cannabis". Alternatively, one could view cannabis leaves as a separate product, containing only the leaves, although this product is not currently widely known or available in this country. The first approach seems more reasonable and is adopted in this proposal. FDA's discussion of cannabis (above) applies equally well to cannabis leaves; FDA therefore proposes to conclude that cannabis leaves have a high potential for abuse.

Alternatively, if "cannabis leaves" are considered to be a separate product, the fourth element identified from the legislative history is applicable. Cannabis leaves are, because of their content of THC, so related in their action to "cannabis," described above, that it is reasonable to assume that there may be significant diversions from legitimate channels (assuming that those diversions became easier than obtaining cannabis from other illicit sources), that there may be significant use contrary to or without medical advice, and the product would have a substantial capability of creating hazards to the health of the user. These conclusions are reached on the basis of the agency's experience with and knowledge of cannabis itself. Under this alternative analysis, FDA again proposes to find that cannabis leaves have a high potential for abuse.

c. *Cannabis seeds capable of germination.* Cannabis seeds capable of germination may be planted and cultivated to produce the cannabis plant. According to one source, the amount of illicit marihuana being grown or produced and harvested in the United States has an estimated value of more than $1 billion per year and is continuing to increase (Ref. 5, Washington Post, November 15, 1981 (F-13)).

When the four elements from the legislative history are applied to cannabis seeds, they would not identify the seeds themselves as having an actual or relative potential for abuse. Thus, there is no evidence that individuals are taking cannabis seeds in an amount sufficient to create a hazard to their health or the safety of others. There is not a significant diversion of cannabis seeds from legitimate drug channels, though it is reasonable to assume that if diversion became easy, it would occur because the seed could be used to grow marihuana. Individuals do not appear to take marihuana seeds on their own initiative. Marihuana seeds do not have an action so related to drugs already listed as having a potential for abuse as to require their identification as drugs subject to abuse.

Yet, Congress in articulating the bases for conclusions concerning the actual or relative potential for abuse of a product did not expect FDA to close its eyes to reality. Cannabis seeds capable of germination can obviously be used to produce cannabis, cannabis resin, and cannabis leaves, all of which plainly present a potential for abuse. For that reason FDA proposes to find that cannabis seeds capable of germination present a significant actual or relative potential for abuse as those terms are used in 21 U.S.C. 811(c)(1).

2. *Scientific evidence of its pharmacological effect if known (21 U.S.C. 812(c)(2)).* House Report 91-1444 (Ref. 4) states "The state of knowledge with respect to the effect of uses of a specific drug is, of course, a major consideration, e.g., it is vital to know whether or not a drug has an hallucinogenic effect if it is to be controlled because of that effect. The best available knowledge of the pharmacological properties of a drug should be considered."

House Report 91-1444 (Ref. 4) states that this factor and factor 3 ("The state of current scientific knowledge regarding the drug or other substance" (21 U.S.C. 811(c)(3))) are closely related. This document distinguishes between factors 2 and 3 in the following manner: The discussion of factor 2 uncritically summarizes the relevant, available scientific evidence. In contrast, the discussion of factor 3 presents the agency's evaluation of what may be reasonably and fairly concluded on the basis of the evidence discussed under factor 2.

a. *Cannabis and cannabis resin.* The voluminous literature on marihuana (over 8,000 references) precludes, for any practical purpose, a complete and systematic review by agency staff of the original references concerning the pharmacological effects of cannabis and its derivatives. The agency, in evaluating the evidence, has reviewed major original articles as well as authoritative secondary sources. Major reviews in the following list are easily available sources of the evidence described in this section.

Institute of Medicine Report, 1982 (Ref. 6).

NIDA Research Monograph, 1980 (Ref. 7).

Addiction Research Foundation, 1981 (Ref. 8).

Journal of Clinical Pharmacology, August-September 1981 (Ref. 9).

"Marihuana," ed R. Mechoulam, Academic Press, 1973 (Ref. 10).

"Pharmacology of Marihuana," ed. Braude and Szara, Raven Press, 1976 (Ref. 11).

Evidence on the effects considered to be related to the use of cannabis is presented in two separate sections: Central Nervous System and Other Major Body or Organ Systems.

Central Nervous System

A. *Cognitive and subjective effects.* Cannabis and its derivatives have been reported to cause disorders in each of the following areas: (1) experience of self, (2) perception and the interpretation of the meaning of perceptions (apperception), (3) thought, (4) feelings and effects, (5) will or volition, (6) control of instinctual behavior or drives, (7) memory, and (8) the higher intellectual functions, which include cognition, reason, and judgment (Ref. 6).

1. *Disordered experience of the self.* Cannabis use can be associated with alterations in the experience of the self in bizarre but well-characterized ways.

For example, depersonalization (the sense that one is not one's normal, natural self) and distortions of body image (the sense that one's body is distorted or different) have been commonly reported in association with the use of cannabis. In the more severe clinical syndromes associated with cannabis use, disturbances in the experience of self of psychotic proportion have been described (e.g., the heart vibrating the entire body, limbs growing longer, the head enlarging). Cannabis use is said to cause distortions in the subjective experience of time and in one's sense of relatedness to the environment (derealization).

2. *Disordered perception and apperception.* Perception and apperception are part of the complex

...y which an individual interacts the environment, obtains (via the ...data about the environment, and ...understand the processed or... a in a normal, meaningful ... Cannabis use has been associated ...ried types of psychopathology ...t perception and apperception. ...ry distortions are commonly ...rted with cannabis use and can ...changes in the intensity or ...lt of perceptions as well as their ...(..., size, shape, proportions). For ...mple, visual images may seem ...ly intense, or three-dimensional ...c may appear flat. Sensory stimuli ...l... misperceived (i.e., illusions) and ...k hallucinations (i.e., perceptions ...a corresponding environmental ...s) may occur. These phenomena ...quite frightening or disturbing to person who experiences them and ...associated with a paranoid ...nce (see discussion below).

...*sturbances of thought.* Two types ...disturbances of thought may be ...ated with the use of cannabis: (1) ...al thought disorder and (2) ...ers of thought content. A formal ...ught disorder consists of several ...phenomena involving ...ments in a person's ability to ...l the sequence, organization, and ...e of thoughts. A formal thought ...often appears to the observer ...ability of a person to ...unicate in a meaningful way. ...eech may seem interrupted in an ...egular and unpredictable manner by ...silences or by illogical, garbled, ...sical, or unintelligible utterances. The disorders of thought content ...sist for the most part of delusions ..., illogical, idiosyncratically held ...s from which the individual cannot ...persuaded by appeals to logic or ...son) or delusion-like beliefs. ...ions may be classified as to their ...ic content or type (i.e., grandiose, ...anoid, etc.). Among the various types ...delusions, those of paranoid character ...obably most important. Because a ...n suffering a paranoid delusion ...ay act upon it as though it were ...ctual, inappropriate aggressive ...havior may sometimes be expressed ...ch persons. Less-organized ...anoid beliefs merge imperceptibly ...ith feelings or moods and are ...ibed in the next section on feeling ...ffects.

4. *Feeling and affects.* Feeling and ...fects (the conscious, subjective ...cts of an emotion) subsume a wide ...ty of moods and states, both ...and dysphoric.

...ria, or a state of elevated mood, ...en reported as a result of cannabis ...This feeling state, variously described as a "high" or as mellow contentment, is thought to contribute to the widespread illicit use of cannabis.

Dysphoric mood states also occur, however. Paranoia, the feeling of being and object of ridicule or persecution, is sometimes reported—especially in persons who may be considered to have less stable personality organizations (i.e., persons more prone to exhibit psychopathology under adverse circumstances). Paranoid experiences and behavior are also reported to be associated with the acute organic brain syndromes (i.e., delirium) attributed to cannabis intoxication. Paranoia may be more organized and take the form of a delusion-like idea or a full-blown delusional system (see discussion above).

Unrealistic fright or fear, sometimes occurring in discrete episodes of overwhelming terror (panics), has been reported to occur in a relatively large proportion (i.e., one-third) of cannabis users (Ref. 6). Lesser degrees of anxiety or dysphoria may occur quite frequently in a large proportion of users. Indeed, intolerance to the dysphoric mood effects of cannabis is said to impair its usefulness as a potential therapeutic agent in many groups (i.e., the elderly).

5. *Disturbances of will or volition.* The "amotivational syndrome" is reported to be a consequence of chronic cannabis use. Apparently, some especially heavy, usually daily, users of cannabis demonstrate a loss of ambition and interest in the more commonly held life goals. Work or school performance deteriorates and the affected person shows features of what might be considered a personality disorder (i.e., apathy, ineffectiveness, inability to plan for the long-term, etc.). Convincing proof that cannabis use is the cause rather than the result of these personality changes is lacking, however, as the evidence is based upon casual clinical observations (case reports).

6. *Disturbances in the control of instinctual urges or drives.* The acutely intoxicated person may, by virtue of organic central nervous system depression or delirium exercise poor judgment and control. The potential for hostile behavior may be increased, especially when the person experiences paranoid feelings in the state of altered consciousness of intoxication caused by cannabis. Aggression is also alleged to occur idiosyncratically, independent of intoxication, in some cannabis users.

7. *Disorders of memory and attention.* Cannabis may alter the ability of a person to attend to a task, to concentrate, to learn new information, to retain that information, or to recall at a later time that information acquired while under the influence of cannabis. Ability to recall information acquired in the intoxicated state may be improved by re-intoxication (an example of state-dependent learning).

8. *Distrubances of higher intellectual functions.* These functions include those of reason, intellect, and judgment. The "amotivational syndrome" can be categorized as an example of this class of pathology, but it has been discussed above as a disorder of volition.

B. *Impairment of motor and psychomotor performance.* General motor coordination may be affected when cannabis is taken in amounts equivalent to that used in social settings. The degree of impairment is dose-related. Reaction time, which is a measure of attentiveness as well as motor agility, may also be compromised. Tracking, the ability to follow a moving target, is impaired at low doses of cannabis intake. Tracking skill is correlated with driving and flying ability (Ref. 6).

Other Major Body or Organ Systems

1. *Cardiovascular.* Acute cannabis use is associated with an acceleration of the heart rate; however, there may be some tolerance to this effect after chronic exposure. In addition, cannabis has effects (these vary with body position, dose, and chronicity of use) on cardiac output, blood pressure, and peripheral vascular resistance (Ref. 6).

2. *Pulmonary.* The effect of cannabis on the pulmonary system is difficult to distinguish from the effects of smoking itself. Cannabis, in small doses, has an acute bronchodilator effect; but this action may, with time, be overshadowed by the irritant properties of smoke which can cause bronchoconstriction. Indeed, chronic smoking of cannabis may cause respiratory system pathology, similar to that produced by tobacco cigarette smoking (Ref. 6).

3. *Reproductive system.* In men, chronic cannabis use may lead to reduced sperm counts and motility; however, the relationship of these changes to male fertility is not known (Ref. 6). In women, there is some reason to believe that cannabis use might contribute to "subfertility," but the evidence to support this belief is indirect (Ref. 6).

4. *Genetic information.* The evidence for a mutagenic effect of delta-9-THC must be distinguished from the mutagenic effect of cannabis when smoked. There is evidence of mutagenicity for the drug when it is smoked. There are also reports of chromosomal breaks occurring in cell

samples obtained from persons using cannabis (Ref. 6).

5. *Immune system.* Cannabis use may be associated with impairment of the function of the immune system (Ref. 6).

b. *Cannabis leaves.* As noted above, cannabis leaves are a constituent of the marihuana product that is normally used both illicitly and in research. Thus, the discussion above is directly applicable to cannabis leaves when viewed in the context in which they have been used. Because cannabis leaves are not known to have been used separated from other parts of the marihuana plant, there is no body of scientific evidence on the pharmachlogical effect of a product containing only cannabis leaves. Because cannabis leaves contain a percentage THC content that is roughly equivalent to the percentage of THC in the cannabis discussed above, however, it is a reasonable scientific conclusion that the effects discussed in the previous section are also those of cannabis leaves alone.

c. *Cannabis seeds capable of germination.* FDA is not aware of scientific evidence of any pharmacological effect of cannabis seeds capable of germination in and of themselves. In fact, because the THC content of the seeds is relatively low, it would not be expected that the seeds by themselves would produce the effects discussed above. On the other hand, as previously noted, the seeds would predictably be used to grow marihuana plants and by that route produce the pharmacological effects discussed in subsection (a) of this discussion.

3. *The state of current scientific knowledge regarding the drug or other substance (21 U.S.C. 811(c)(3)).* as noted previously, this discussion presents FDA's evaluation of the evidence discussed under factor 2 above.

a. *Cannabis and cannabis resin.* In weighing the scientific evidence on the effects of cannabis use, the agency has concluded that much of what is said and written about the plant and its derivatives is unsupported testimony and argument. Such evidence cannot be used to estimate rates of risk for specific effects or establish cause and effect relationships. It is not known what proportion of a representative sample of normal persons would experience many of the effects described in the preceding section. The relationship of the observed effects of cannabis to the quantity of drug consumed and to the duration of its use is not always evident. Moreover, the mere association of a drug with a phenomenon does not demonstrate that the drug caused the phenomenon. The putative drug effect may be merely coincidentally associated with drug use.

In light of these many qualifications about the nature of the available scientific evidence, it is important to explain how the agency distinguished reliable from unreliable information and reached its conclusions about the "state of current scientific knowledge regarding" cannabis.

First, members of the agency's staff who are expert in issues of illicit drug use and the requirements for scheduling recommendations relied upon their own experience and knowledge of cannabis and experience in reviewing other scheduled drugs to reach their conclusions.

Second, the expertise of the agency's expert staff and other appropriate agency officials has been supplemented with expertise from specific experts on cannabis who are or where either special government employees or members of the agency's Drug Abuse Advisory Committee.

Finally, the agency has relied upon the scientific literature. Recent published evidence reviewed by the agency includes the report by the Institute of Medicine (IOM), National Academy of Sciences, on *Marihuana and Health* (National Academy Press, Washington, 1982) (Ref. 6). The IOM report is not only recent and comprehensive but the IOM committee that wrote the report appears to be an impartial and disinterested group of scientists whose goal was an accurate statement of our current knowledge about the relationship of cannabis use to the public health.

FDA's conclusion about the state of current scientific knowledge regarding cannabis follows; they are organized by body or organ system in a manner that parallels the presentation of the evidence under factor 2.

Central Nervous System

Although the agency has no means to estimate the exact proportion of cannabis users that will be affected, there is little reason to doubt that cannabis has potent effects on psychological and neurological behaviors of people. Available evidence shows that cannabis use can alter perception (cause illusions and hallucinations) and mood (cause anxiety, dysphoria, paranoia, etc.), and can cause panic and reactions of psychotic degree. Cannabis use can impair motor and psychomotor performance, and can alter the level of consciousness, impulse control, and, perhaps, judgment. The acute effects of cannabis range from mild, subjectively pleasing changes in affective state to frank, organic delirium. The acute behavioral effects are linked to cannabis use in a causal way. In contrast, evidence on the long-term adverse consequences is less persuasive. In particular, it is not clear whether the well-characterized "amotivation" syndrome associated with chronic, heavy marihuana use is a manifestation of the personal character or psychopathology of some marihuana users or an expression of drug effect.

Body Systems Other Than the Central Nervous System

Cannabis has effects on the heart, lungs, and endocrine systems. The magnitude and significance of these effects is not known, but each must be considered a possible potential risk to the public health.

In summary, the effects of major social and medical significance associated with cannabis use and important to a scheduling recommendation are largely related to the central nervous system but include the cardiovascular and pulmonary systems. Cannabis does not appear to have major effects of known significance on other organ systems. It is important to emphasize, however, that the available evidence often does not address the critical questions.

The agency agrees with the general conclusion of the IOM (Ref. 6) that, "[t]he scientific evidence published to date indicates that marihuana has a broad range of psychological and biological effects, some of which, at least under certain conditions, are harmful to human health. Unfortunately, the available information does not tell us how serious this risk may be" (p. 5).

b. *Cannabis leaves.* The conclusion in the previous discussion concerning cannabis and cannabis resin applies to cannabis leaves for the reasons and to the extent stated in this document's discussion of Factor 2 as it applies to cannabis leaves. Current scientific knowledge concerning cannabis leaves not in conjunction with other parts of the marihuana plant is totally undeveloped because the leaves are not used separately.

c. *Cannabis seeds capable of germination.* Although current scientific knowledge concerning the pharmacological effects of cannabis seeds is undeveloped, because the THC content of the seeds is relatively very low, it can be fairly concluded that the seeds themselves will not have the pharmacological effects associated with other parts of the marihuana plant. As previously noted, however, the pharmacological effects of cannabis discussed above, may be said to be associated with the seeds in that the

rds will likely be used to grow the
int

a. history and current pattern of use (21 U.S.C. 811(c)(4)). In the gis. e history of the CSA, Congress m- ented on Factor 4 as follows: "To te aine whether or not a drug should c trolled, it is important to know e pattern of abuse of that substance, cl ling the social, economic, and xol gical characteristics of the eg ents of the population involved in ich abuse."

T following information en nstrates a history and current attern of widespread illicit use of annabis in the United States, as ie ured by wide use and illegal np rtation and distribution.

a. Cannabis and cannabis resin. Cannabis use goes back to the beginning of recorded history. For example, ar abis preparations have been used or thousands of years in Asia. Cannabis spread West to Europe and by the time Eu peans reached the New World, they we using the cannabis plant as a source of cloth and as an intoxicant. Marihuana or cannabis use began to gr in popularity in the United States du ng the 1920's. By 1927, 46 States and the District of Columbia had passed law against marihuana and in the same ye ie Federal government enacted th arihuana Tax Act. This Act made registration and taxation of marihuana buyers and sellers mandatory, and in osed criminal penalties. The Act ef ctively banned the possession and use of cannabis preparations. Subsequently in 1961, it was controlled u er the Single Convention on Narcotic D gs. In the United States, it was subsequently controlled under Title II of the Comprehensive Drug Abuse P vention and Control Act of 1970.

There have been a number of studies on the pattern of use and abuse of cannabis related to the pattern of use of o er drugs of abuse. These studies s ow that cannabis is used concurrently with alcohol or other drugs of abuse (e.g., Ref. 13).

Results from a 1979 survey on drug u reported by the National Institute on Drug Abuse (Ref. 14) were as follows: in 1979, 8 percent of 12 and 13 year-olds r ported some experience with c nnabis, and by ages 14 and 15, the percentage who had used cannabis increased to 32 percent. More than half (percent) of 16 and 17 year-olds had ed cannabis. In the overall 12 to 17 y -old group, 31 percent had "ever e ienced" marihuana use, more than ouble the figure (14 percent) which was ported in 1972. The peak use was in the age group from 18 to 25 years: 68 percent in 1979 compared with 48 percent in 1972.

With respect to current use of cannabis, defined as use within the month preceding the survey, 16.7 percent of the 12 to 17 year-old group in the 1979 survey currently used cannabis, while 35 percent of the 18 to 25 year-old group were currently using cannabis. In the 1979 survey, in the age group 26 years and over, 19.8 percent reported ever having used cannabis, while 6 percent reported current use. Corresponding figures for 1972 were 7.4 percent for having experienced cannabis use and 2.5 percent currently using cannabis. Current users age 12 to 17 in 1972 represented 7 percent of that age group, while in 1979 that same group (now members of the 18 to 25 year-old group) had a current use rate of 35 percent. Thus approximately 28 percent of the individuals who were current users between the ages of 18 and 25 in 1979 (the differences between 7 percent and 35 percent) began using after the age of 17.

A similar study, using different age parameters and focusing on the year 1977, provides confirmatory data. According to the NIDA Research Monograph, No. 35, May 1981 (Ref. 15), in 1977 there were 9,632,000 (56.8 percent) out of 16,958,000 young adults age 18 to 21 years, and 9,261,000 (60.3 percent) out of 15,358,000 young adults age 22 to 25 years who reported ever having used marihuana. These rates represent increases of 4 percent and 13 percent over the 1974 rates for 18 to 21 years and 22 to 25 years, respectively. The survey indicates there were 3,233,000 regular users of marihuana out of 13,415,000 (24.1 percent) age 18 to 25 years in 1977.

The special problem of drug abuse among women was reported in 1980 (Ref. 16). Results were obtained from a sample of 14,428 women clients in treatment centers. The paper addressed differences in use of heroin, marihuana amphetamines, barbiturates, and sedatives according to age, race, and education. Marihuana was the second most commonly abused drug among these women.

A special U.S. population that has been surveyed is the military. "Highlights from the Worldwide Survey of Nonmedical Drug Use and Alcohol Use Among Military Personnel, 1980" (Ref. 17). For the total military, 27 percent reported using any drug within the past 30 days, and 26 percent reported using marihuana or hashish within the past 30 days. Twenty-six percent reported using marihuana, or hashish, during the past 30 days. Thirty-six percent reported using any drug during the past 12 months, while 35 percent reported using marihuana or hashish during the past 12 months. Further, for the total military, 19 percent of the population reported using marihuana or hashish at least once a week during the past 30 days. The next closest drug group used frequently by the military was amphetamines or other stimulants, at the rate of 3 percent at least once a week during the past 30 days. Cannabis, i.e., marihuana or hashish, is thus by far the most widely abused drug in the military.

The National Institute on Drug Abuse (NIDA) also has reported on demographic trends in drug abuse, 1980–1995 (Ref. 15). In this report, NIDA uses information from previous surveys, up to the 1977 survey, to predict illicit drug use for the next 10 to 15 years. NIDA concluded that illicit drug use is decreasing among all age groups.

b. Cannabis leaves. The discussion above of the history and current pattern of abuse of cannabis and cannabis resin applies to cannabis leaves as commonly used. FDA is unaware of any significant history of use of cannabis leaves separated from all other parts of the marihuana plant.

c. Cannabis seeds capable of germination. The discussion above on the history and current pattern of abuse of cannabis and cannabis resin applies to cannabis seeds capable of germination because cannabis may be produced by use of such seeds. FDA is unaware of any history or current pattern of abuse of the seeds other than their use to grow cannabis.

5. The scope, duration, and significance of abuse (21 U.S.C. 811(c)(5)). In House Report 91-1444, Congress stated that:

> In evaluating existing abuse, not only must the Attorney General know the pattern of abuse, but he must also know whether the abuse is widespread. He must also know whether it is a passing fad, or whether it is a significant chronic abuse problem like heroin addiction. In reaching his decision, the Attorney General should consider the economics of regulation and enforcement attendant to such a decision. In addition, he should be aware of the social significance and impact of such a decision upon those people, especially the young, that would be affected by it.

a. Cannabis and cannabis resin. The discussion in the previous section of percentages of marihuana users demonstrates that the cannabis abuse is of wide scope, involving, among others, the young and members of the military, is of considerable significance, and has continued for over a decade. Further

evidence on cannabis abuse is provided by information concerning the total amount of cannabis available in this country from illicit sources.

According to the Drug Enforcement Administration (DEA), about 10,000 to 15,000 metric tons of cannabis (marihuana) were smuggled into the United States in 1978, a 4 percent increase over the 12,000 metric tons smuggled in 1977 (Ref. 20). The value of the marihuana in 1978 was estimated by DEA to be $15 to 23 billion (approximately $19,000,000,000 in 1977) (id).

For 1979, DEA has estimated the total cannabis supply to be between 10,000 and 13,600 metric tons. Seventy-five percent of the total cannabis in 1979 was from Columbia, 11 percent from Mexico, 7 percent from Jamaica, and 7 percent from domestic U.S. sources. For the year 1980, the current estimate is 10,600 to 15,500 metric tons. Columbia supplies 75 percent, Mexico 9 percent, Jamaica 10 percent, and domestic U.S. sources account for 6 percent. The total amount would convert to 23,320,000 to 34,100,000 pounds of cannabis available in the United States in 1980. This amount compares with the estimated 24,000,000 pounds available in 1977. The amount of cannabis grown for scientific and medical investigations in the United States in 1979 was 986 kilos or 2,100 pounds and approximately 2,000 kilos or 4,400 pounds for the year 1980.

These statistics show that the scope of the illicit cannabis traffic is significant, and has been significant for a least 5 years. Also, the extent of the illicit use of cannabis, particularly among the young and the young adults, is widespread throughout the United States. Further, these statistics show that the drain of funds into illicit channels as a result of cannabis use is significant.

b. *Canabis leaves.* The discussions above regarding the scope, duration, and significance of abuse for cannabis and cannabis resin apply to cannabis leaves when used in conjunction with other parts of the marihuana plant. FDA is unaware of any use of cannabis leaves separated from all other parts of the marihuana plant and the agency, thus, has no information about scope, duration, and significance of abuse of leaves separated from other parts of the plant.

c. *Cannabis seeds capable of germination.* There are no data concerning the extent of illicit traffic in cannabis seeds capable of germination. As discussed previously, there are no data available on abuse of the seeds per se, as opposed to the plants that may be grown from the seeds.

6. *What, if any, risk there is to the public health (21 U.S.C. 811(c)(6).* With respect to this factor, House Report 91-1444 states: "If a drug creates no danger to the public health, it would be inappropriate to control the drug under this bill."

a. *Cannabis and cannabis resin.* Under factors 2 and 3 above, the scientific evidence of the pharmacological effects and the state of current scientific knowledge regarding cannabis are discussed in detail. The agency agrees with the general conclusions of the IOM (Ref. 6) that, "[t]he scientific evidence published to date indicates that marijuana has a broad range of psychological and biological effects, some of which, at least under certain conditions, are harmful to human health. Unfortunately, the available information does not tell us how serious the risk may be" (p. 5).

The adverse consequences associated with marihuana use include both acute and chronic effects. The acute health hazards are most important and include, among others, impairments in almost all aspects of central nervous system function, and decrements in psychomotor performance skills necessary for driving or flying. Certain cardiovascular effects (e.g., those that can lead to increased heart rate and associated circulatory changes) may be harmful, especially to those with pre-existing heart disease. The acute health hazards often result in medical problems requiring immediate medical attention at hospital emergency rooms.

The chronic hazards of marihuana use are less well established. One probable risk of importance is the one associated with the common route of cannabis administration, smoking. Smoking of tobacco cigarettes is a well-documented health hazard, and it is reasonable to assume that smoking of cannabis cigarettes is hazardous as well.

Much of the most recent evidence about the effects of marihuana use in humans is reported in the Addiction Research Foundation Report, 1981 (Ref. 8) prepared by internationally recognized scientists in the field of drug abuse and effects of marihuana and the Institute of Medicine Report, 1982 (Ref. 6), previously discussed. The National Institute on Drug Abuse also provided much of the most recent information relative to the epidemiology of effects of cannabis on the public use. The risk to the public health from acute and chronic cannabis use is evaluated on the basis of the effects included in these reports. Also, as is discussed in Part III below, cannabis or marihuana has no currently accepted medical use in treatment in the United States. Thus, in weighing the risks against the benefits of marihuana use, FDA proposes to conclude that the scale is tipped heavily towards the risk. Clinical investigations designed to determine whether marihuana has medical utility and whether marihuana may be used safety under medical supervision are still ongoing.

In estimating the number of individuals who use cannabis and, thus, are at risk of suffering the reported adverse health consequences, the Federal government uses data from several sources including certain surveys, including the Drug Abuse Warning Network (DAWN), the National Household Survey on Drug Abuse (Household Survey), and the High School Senior Survey (High School Survey). DAWN represents an ongoing reporting system, while the Household Survey and the High School Survey are periodic data collection efforts. Each survey contributes valuable information to the overall drug abuse picture.

The reports of death from medical examiners collected by DAWN for the calendar year 1980 placed marihuana the lower end of the spectrum of frequency among the 100 drugs or substances reported. During the same period, however, marihuana was listed at the top end of the spectrum of frequency among the 100 drugs or substances reported as the reason for emergency room visit during this period (Ref. 21). Marihuana was, for example, mentioned more than twice as often as amphetamines. Thus, it would appear that the adverse effects from marihuana use rarely result in a fatal outcome but are serious enough to be one of the major drug causes for seeking emergency room treatment.

In the High School Survey, high school seniors reported that they believe the regular use of marihuana has caused them to experience significant problems. For example, 28 percent reported they think less clearly, while 11 percent reported they felt less stable emotionally. Young people are believed to be especially at risk from the use of marihuana because of their ongoing physical and emotional maturation. It is possible that young, regular marihuana users may not be able to develop appropriate "life skills" on schedule, and that failing to do so it may be difficult, if not impossible, for them to make up these developmental differences later in life (Ref. 12).

As discussed earlier, although certain adverse effects have been reported from cannabis use, the exact percentage of cannabis users who are experiencing these adverse effects is unknown. FDA tentatively concludes that the risk to

: health from marihuana use is ularly serious because the number ril ana users is so large. ev the precise risk, widespread f c ibis will obviously produce ate, cidence of harm than ve little use of cannabis. ov , although in some cases the cons ip of cannabis use to reported se effects is not certain, cr dy the emotional and tir tional" effects, the equences of these effects, if real, o great that, in the absence of good en against the reported cis on, the risk to the public health be considered great. FDA's osed conclusion that cannabis does te significant risk to public health us ased on its known adverse cts and adverse effects that are ested but not yet proved to be et o marihuana use, both in a ng f relatively widespread use. sed on the 1979 Household Survey, agers in the United States use more hi na than teenagers anywhere in e world (Ref. 22). Although a nt trend shows that marihuana use use of other drugs has declined, it is ea y to tell whether this decrease ce tinue or is merely a pause in the Despite this recent trend, the all valence of use of marihuana re ed at approximately 60 er of high school seniors for the s 1978, 1979, and 1980 (Ref. 6). ently, it is estimated that 22 million bo t 10 percent of the total U.S. ul on now use marihuana (Ref. 22). 960, less than 7 percent of young lts age 18 to 25 had used marihuana. 97 more than 60 percent of young lts ad used marihuana (Ref. 22). DA, thus, proposes to conclude that nabis may produce significant er health effects to persons who m rihuana. And, because roximately 22 million Americans are rted to be current users of ih ana, FDA proposes to conclude t re is a significant risk to the lic health from marihuana or nabis use.

. (nnabis leaves. The risk to the li ealth associated with use of nabis leaves in the state in which y are normally found, i.e., in ju tion with others parts of the il ana plant, is significant for the ons stated in subsection (a) above. re is virtually no reported er nce with a product containing n is leaves separated from all other ts r e marihuana plant. Because le themselves have significant C ntent, however, it is reasonable co lude that a use of a leaf-only product would present the same risk as use of cannabis itself.

c. *Cannabis seeds capable germination.* The risk associated with cannabis seeds derives only from the probability that such seeds would be used to grow marihuana, which would in turn produce the risks described above.

7. *Its psychic or physiological dependence liability (21 U.S.C. 811(c)(7)).* In House Report 91-1444, Congress states that "There must be an assessment of the extent to which a drug is physically addictive or psychologically habit-forming, if such information is known."

a. *Cannabis and cannabis resin.* (1) *Psychological (psychic) dependence liability.* In the Federal Register of March 9, 1982 (47 FR 10083), FDA proposed to conclude that some individuals should be considered sufficiently strong drug-seeking in their behavior to be considered severely psychologically dependent on cannabis. The basis for this conclusion is our belief that repeated seeking of an illicit drug with an established potential to cause injury constitutes prima facie evidence of psychological dependence. Also, it should be noted that a report of the American Medical Association's (AMA) Council on Scientific Affairs, as adopted by the AMA House of delegates, concluded that marihuana is hazardous to health and that there was a growing prospect of appreciable number of marihuana users incurring physiological and psychological impairment (Ref. 23). Since the March 9, 1982 Federal Register publication, FDA has completed a review of two recent and significant reports on marihuana and health (Institute of Medicine Study and Addiction Research Study) (Refs. 6 and 8). These reports include nothing that changes FDA's earlier proposed conclusions. Thus, FDA proposes to conclude that marihuana use can result in severe psychological dependence.

(2) *Physical (physiological) dependence liability.* The agency defines physiological dependence as the appearance of a characteristic syndrome, consisting of physical signs and symptoms, that appears upon cessation of drug use. Only one investigator has reported withdrawal signs and symptoms after frequent large doses of THC (Ref. 11). Other investigators have failed to observe a withdrawal syndrome. However, it is important to emphasize that drugs now well known to cause physiologic dependence (such as barbiturates, benzodiazepines, amphetamines, and some mixed opioid agonist/antagonist analgesics) were for many years assumed to be free of any such liability. It was only after many years of medical use, under conditions of close scrutiny, that the serious physiological dependence caused by these drugs was recognized. Thus, although the agency is unable to conclude at this time, on the basis of the evidence available, that cannabis produces physiologic dependence, the experience with known dependence-producing drugs (described above) must be considered.

b. *Cannabis leaves.* For the reasons discussed above, cannabis leaves present a psychological dependence liability. This conclusion necessarily follows from the evidence concerning cannabis, whether the leaves are considered as components of marihuana as generally used or as a separate product that, because of its THC content, would have the same effects as cannabis. Like cannabis, cannabis leaves cannot now be considered to have a physiological dependence liability.

c. *Cannabis seeds capable of germination.* As previously noted, the seeds do not themselves present a dependence liability, but, because they may be used to grow marihuana, have a liability associated with that fact.

8. *Whether the substance is an immediate precursor of a substance already controlled under this title (21 U.S.C. 811(c)(8).* House Report 91-1444 states that "The bill allows inclusion of immediate precusors on this basis alone into the appropriate schedule and thus safeguards against possibilities of clandestine manufacture."

a. *Cannabis and cannabis resin.* Cannabis and cannabis resin are not precursors of any substance already controlled. Cannabis and cannabis resin are substances which are themselves already controlled in Schedule I of the Controlled Substances Act.

b. *Cannabis leaves.* Cannabis leaves are not an immediate precursor to a substance already controlled under this title. Because they are viewed as a component of cannabis, they are already controlled in schedue I.

c. *Cannabis seeds capable of germination.* Cannabis seeds capable of germination are not an immediate chemical precursor to a substance already controlled under this title. They are a "precursor" of cannabis in the sense that cannabis may be grown from the seeds. Because they are a component of cannabis, they are already controlled in schedule I.

III. Criteria For Scheduling

The eight factors described above are used to determine into which of the five

CSA schedules, if any, a given drug or substance should be placed. Each of the five CSA schedules (I to V) has three criteria (A to C) to aid in this determination. To assign a substance to a schedule, the Attorney General must find that the substance meets the statutory criteria for that schedule. See 21 U.S.C. 811(a).

Criterion A for all five schedules is a series of descriptions of abuse potential, declining from high to low abuse potential. Schedules I and II are identical in this regard, both requiring a finding of "high" potential for abuse. Schedules III through V require findings of lower, though still some, abuse potential.

Criterion B for all five schedules deals with whether the drug, or other substance, has a currently accepted medical use. Schedule I drugs must be found to have "no currently accepted medical use in treatment in the United States" while schedules II through V all require a "currently accepted medical use * * *." In addition, criterion B for schedule II allows an alternative finding: "currently accepted medical use with severe restrictions."

Criterion C is different for schedule I than for the other schedules. For schedule I, the criterion requires a finding of "lack of accepted safety for use of the drug or other substance under medical supervision." For schedules II through V, this criterion consists of a sliding scale of the drug's dependence-producing capacity, either physical or psychological. Schedule II drugs require a finding of the highest dependence-producing capacity while schedule V drugs require the lowest.

In the Federal Register of June 20, 1979 (44 FR 36127), DHHS stated that it believed, from a medical/scientific standpoint, that the marihuana (or cannabis) plant materials "could be placed in either schedule I or schedule II" but recommended continued control in schedule I. A factor in the determination that both schedules I and II were appropriate from a medical scientific standpoint included the statements that: "Conceivably, the current investigational use of some of the substances could be classified as 'a currently accepted medical use with severe restrictions' within the meaning of the second criterion for schedule II. That is a plausible interpretation of that criterion but its appropriateness is not free from doubt." (It should be noted that these statements were made in the context of the 1979 proceedings which applied to THC as well as the marihuana (or cannabis) plant materials at issue here.)

Although certain developments have occurred with respect to these substances in the intervening years (i.e., Federally approved research continues, legislation in some States provides for various degrees and kinds of research controls, and FDA has approved, on the recommendation of its oncologic drugs advisory committee, THC distribution under the National Cancer Institute's "Group C" system), these developments do not change the fact that, as explained below, in FDA's opinion the marihuana plant materials, as opposed to THC, meet all three criteria only for schedule I. Accordingly, FDA proposes that they remain in schedule I.

A. *Criterion A*—On the sliding scale of abuse potential, FDA proposes to conclude that cannabis, cannabis resin, cannabis leaves, and cannabis seeds capable of germination (because they are planted, cultivated, grown, and harvested to produce the plant) have a high potential for abuse and thus meet this criterion for schedules I and II (the criterion is identical for these two schedules).

As plant constituents, these cannabis substances have been shown to have a high potential for abuse (see discussion in factor 1 above). Thus, although licit plant materials have not been abused because they have been subject to stringent controls as an investigational drug under the Federal Food, Drug, and Cosmetic Act and a schedule I substance under the CSA, illicit plant materials are widely abused. These substances have marked psychotropic effects and, if more freely available, their abuse would very likely increase as major drugs of abuse (see discussions in factors 4 and 5). If the stringent CSA controls are removed from these substances, it can be anticipated that there would be attempted thefts, that attempts would be made to divert the drug from legitimate channels, and that any drug so diverted would command premium prices in the illicit market.

The tentative conclusion that these substances have a high potential for abuse (thus meeting criterion A for schedules I and II) logically precludes them from meeting criterion A for schedules III through V, for drugs in each of these three schedules have a progressively lower abuse potential than schedule I and II drugs.

B. *Criterion B*—This criterion involves the "accepted medical use" of the drug and has three different variations among the five schedules, as follows:

1. *Schedule I:* "The drug or other substance has no currently accepted medical use in treatment in the United States."

2. *Schedule II:* "The drug or other substances has a currently accepted medical use in treatment in the United States *or* a currently accepted medical use with severe restrictions." (Emphasis added.)

3. *Schedules III through V:* "The drug or other substances has a currently accepted medical use in treatment in the United States."

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. The agency stated this interpretation previously in the Federal Register document dealing with THC (47 FR 10084). NORML, in a subsequent action brought in the United States Court of Appeals for the District of Columbia, challenged that interpretation as conflicting with a statement made by the court in a footnote in *NORML* v. *DEA*, *supra*, 559 F.2d at 750, n.85. In the footnote, the court noted that the interrelationship between the Federal Food, Drug, and Cosmetic Act, in particular its "new drug" approval provision, and the Controlled Substances Act was far from clear. The court stated that it was appropriate for NORML to apply for rescheduling of marihuana under the Controlled Substances Act before obtaining approval of a new drug application under the Federal Food, Drug, and Cosmetic Act. *Id.*

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, see, 21 U.S.C. 321(p)(1) and Pub. L. 87-781, sec. 107(c)(4). It is obvious, however, that the marihuana substances at issue here would not qualify either for exemption from the "new drug" definition or for the "grandfather clause" exceptions to premarket clearance.

A drug may also, theoretically, be legally marketed without violating the Federal Food, Drug, and Cosmetic Act if it is manufactured, processed, and used entirely within a single State without any connection at all with interstate commerce. (See, however, Article 23 and 28 of the Single Convention on Narcotic Drugs regarding restrictions imposed by treaty on manufacture of marihuana.) The agency has considered whether there is any basis to conclude that the

ances at issue in this document obtained "accepted medical use" tu of totally intrastate production se d has found no basis for a us hat these products have nec acceptance of their medical y at means.

is here is no reason to conclude he marihuana substances at issue would qualify for "accepted ca se" in the absence of the ov by FDA of an NDA.

e mechanism set up by Congress wful marketing of a new drug re submission of an NDA to FDA T approval of that application e marketing. Before FDA can ov an NDA, however, the drug sc must submit data from an is e battery of experimental ig on both animals and humans to lish the drug's safety and ti ness for its proposed uses. In tic , the sponsor must submit data anufacturing controls onstrating that standards of it strength, quality, and purity be met. Finally, the sponsor must mit labeling which adequately ct the proper conditions for use. 21 U.S.C. 355(d) and 21 CFR 314.1.

/ er FDA has evaluated this mation can the agency make a sio whether the NDA should be o nd the drug marketed.

u the lack of an approved NDA drug substance leads FDA to find that substance lacks an "accepted ic use in treatment" for two or First, if use of the drug is wful whenever interstate commerce ve ved, medical use of the drug ic be classified as accepted. on in the absence of the data ssary for approval of an NDA, the ic has no basis for concluding that ic use of the drug in treatment can o idered acceptable by medical dards.

ic use "currently accepted medical " (schedules III through V s edule II, first clause) means ully marketed under the act, "no er ly accepted medical use " an not lawfully marketed. The st ces at issue fit into the later gory because they are new drugs in the meaning of the act and there ot n approved NDA for the drugs. s, ey cannot be legally marketed out an approved NDA. The lack of m any sources demonstrating t of these substances is medically p able, i.e., that sufficient data ts alify the substances for NDA c confirms the finding that these it ces do not meet this criterion for dules III through V. Therefore, these substances meet criterion B for schedule I.

A plausible argument exists, however, that these substances also meet the second clause of criterion B for schedule II because they have "a currently accepted medical use with severe restrictions." Although this clause is not defined in either the statute or the legislative history, the agency believes that only certain investigational drugs in the later stages of the investigational process may fall within this statutory language.

Investigational drugs progress from experimentation in a very limited, closely supervised setting involving only a few individuals to use in a broader investigational protocol using hundreds of patients. Under FDA's regulations, reports of these clinical studies are periodically sent to FDA so that the agency can monitor properly the ongoing research and progression to broader clinical trials. See 21 CFR Part 312.

The placement of THC in National Cancer Institute's "Group C" distribution scheme is an example of clinical research progression that qualifies as a "currently accepted medical use with severe restrictions." See 47 FR 10080, March 9, 1982. Clinical research on the marihuana (cannabis) materials at issue, however, has not progressed to the point that FDA believes that they have a currently accepted medical use with severe restrictions. In typical drug development, following studies in animals, studies in humans are conducted in phases or stages to provide necessary information. The information gathered at each phase must be evaluated and determinations made based on the evaluation before a subsequent phase may begin. Early phase studies usually involving small numbers of patients are necessary to provide initial evidence as to safety, pharamacological effects, and dose-related side effects, principally so that later studies can be carefully designed. Subsequent phases of studies are necessary to provide evidence of clinical safety and effectiveness, i.e., knowledge of effective dose and side effects and indications of therapeutic potential in humans. Later phases of studies are conducted to confirm and extend the findings indicated by earlier phase studies. In later phases a drug is used the way it would be administered when marketed. By the time these later studies are completed, the drug or substance usually has been studied in several hundred to several thousand patients. Generally by this time sufficient data have been generated to that FDA can make a determination regarding whether the drug is safe and effective under the statutory definitions. See 21 U.S.C. 355(d).

THC is a drug in the late phases of investigation as described above while the investigational studies on the marihuana plant materials are properly classified as in the earlier phases of study. Moreover, before a drug substances may be used in the practice of medicine it must have a composition of active ingredients that has been established and accepted as standard (for example, conjugated estrogens and powdered digitalis). Such standardized identity, purity, potency, and quality are specified either in a new drug application or in official compendium, e.g., U.S. Pharmacopeia or National Formulary. There is no standard cannabis substance.

Legislation in more than 20 States authorizes the use of marihuana and/or THC for medical research, primarily to combat nausea and vomiting associated with cancer chemotherapy and in the treatment of glaucoma. Such uses, however, should not be confused with the "accepted medical use" standard. These uses are all investigational uses. At least 11 States FDA-approved protocols for such investigations. The American Medical Association's Council on Scientific Affairs, in its report entitled "Marihuana in the '80s" (Ref. 23), makes the following statement: "For those [s]tates with enabling legislation that has not as yet been implemented, it is recommended that appropriate regulations and guidelines be established to insure that bonafide research is carried out, and that medical use beyond the context of clinical investigation is not permitted." This statement clearly is in accord with FDA's view that cannabis materials, as investigational research substances, are without accepted medical use in therapy or treatment by physicians practicing medicine in the United States.

Such State legislation, often referred to in their titles as "Therapeutic Research Acts," should not be confused with State laws which "decriminalize" the possession or transfer of certain marihuana materials for personal use, including recreational uses. These latter State laws involve reductions in criminal penalties and do not address medical research with these substances. Consequently, FDA tentatively concludes that although an argument that the second clause of criterion B for schedule II might be bet by certain marihuana substances under investigational use, the marihuana

substances at issue here do not meet criterion B for schedule II.

C. *Criterion C*—FDA proposes that the substances at issue meet criterion C for schedule I because there is "a lack of acccepted safety for use of the drug or other substance under medical supervision." FDA believes that "accepted safety," like "accepted medical use," has not been shown for a drug product that has not qualified for lawful marketing under the act. Accordingly, because these substances are not lawfully marketed, there is a "lack of accepted safety * * *."

As noted above, 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). Because 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 the labeling. For this reason, FDA requires, before approval of an NDA, that extensive clinical and preclinical testing be conducted to establish the safety of the drug. Indeed, FDA must deny approval of an NDA if inadequate information about the drug's adverse reactions is presented. See 21 U.S.C. 355(d)(1).

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. Physicians depend on detailed labeling for information on when and how a drug should be used, and any claim in the labeling must be supported by clinical studies. False or misleading proposed labeling also precludes FDA approval of an NDA. 21 U.S.C. 355(d)(6).

Clearly, the further along a drug is in the investigational process, the more information about safety and effectiveness there will be. But it is only upon approval for marketing, when there has been an institutional decision based on scientific judgment 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.

The safety and efficacy of the cannabis materials at issue have not yet been fully studied. Indeed, these materials are currently distributed to a limited number of physicians and several States as investigational new drugs only, and a considerable amount of clinical research is still needed before an NDA could be submitted. Only when full information is received and reviewed by FDA can a responsible, scientific judgment be made that marihuana materials have "accepted safety for use * * * under medical supervision". Accordingly, under the present facts, FDA proposes that the cannabis substances at issue meet criterion C for schedule I.

Criterion C for schedule II provides that "[a]buse of the drug or other substance *may* lead to severe psychological *or* physical dependence" (emphasis added). FDA proposes that abuse of the substances at issue may lead to severe psychological dependence in some individuals (see discussion in factor 7). Whether this psychological dependence might be better characterized as "high" (schedule III criterion) rather than "severe" (schedule II criterion) is a matter of scientific judgment. However, FDA tentatively concludes, based on the information before it, that the psychological dependence-producing ability of these substances lies at the top end of the spectrum and is most appropriately characterized as "severe," thereby meeting the criterion for schedule II.

In terms of possible physical dependence, FDA believes the available information before it, at this time, is insufficent to determine with certainty whether physical dependence occurs.

D. *Summary chart.* FDA's proposed recommendations on scheduling criteria for cannabis, cannabis resin, cannabis leaves, and cannabis seeds capable of germination may be summarized in the following chart:

Note.—The criterion varies according to the schedule.)

	Criterion A	Criterion B	Criterion C
Schedule I	Met	Met	Met.
Schedule II	Met	Not met	Met.
Schedule III	Not met	Not met	Possibly met.
Schedule IV	Not met	Not met	Not met.
Schedule V	Not met	Not met	Not met.

E. *Conclusion.* FDA proposes to recommend that, based on the scientific and medical evaluation, each of the cannabis materials at issue meet all three criteria for schedule I. FDA proposes to recommend that each of the cannabis materials at issue remain in schedule I.

IV. Public Hearing

Under 21 CFR Part 15, the Commissioner of Food and Drugs may, as a matter of discretion, permit persons to present information and views at a public hearing on any matter pending before FDA. The Commissioner has concluded that it is in the public interest to hold such a public hearing for the purpose of obtaining information and views on the material in Parts II and III above concerning the appropriate scheduling status under the CSA of cannabis, cannabis resin, cannabis leaves, and cannabis seeds capable of germination.

The public hearing will be be held on September 16, 1982, from 9 a.m. to 4 p.m. in Conference Rms. D and E, Parklawn Bldg., 5600 Fishers Lane, Rockville, MD 20857.

Every effort will be made to accommodate each person who wants to participate in the public hearing. However, each person who wants to ensure his or her participation in the hearing is encouraged by close of business on August 27, 1982, to: (a) submit the text of the presentation so that the presiding officer and any other persons who may serve on a panel conducting the hearing may formulate useful questions to be posed at the hearing (a comprehensive outline may be submitted as an alternative to the text); and (b) file a written notice of participation containing the name, address, phone number, affiliation, if any, of the participant, topic of presentation, and approximate amount of time requested for the presentation. Oral notice of participation may be made by telephone as an alternative to the written notice.

The text or comprehensive outline and the written or oral notice of participation may be made to: Frederick J. Abramek, Bureau of Drugs (HFD-120), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3800.

Shortly after August 27, 1982, the amount of time allotted to each person and the approximate time that oral presentation is scheduled to begin will be determined. A hearing schedule showing the persons making oral presentations and the time allotted to each person will be filed with the Dockets Management Branch (address above) and mailed or telephoned to each participant before the hearing. If the number of persons formally requesting time for presentation exceeds the number that can be accommodated during the day session, the hearing will be carried over past the scheduled time and, if necessary, to the following day. An attempt will be made to hear, at the conslusion of the hearing, any person who is late. Other interested persons attending the hearing who did not

u[illegible] an opportunity to make an oral sentation will be given an portunity to make an oral [illegible]tation at the conclusion of the [illegible] in the discretion of the [illegible] officer, to the extent that time [illegible]. The hearing will be informal in [illegible] and the rules of evidence do not pl[illegible]

ferences

T[illegible] following information has been [illegible]c[illegible]d in the Dockets Management anch (address above) and may be en by interested persons from 9 a.m. 4 [illegible]m., Monday through Friday.

1. [illegible]arihuana and Health, 8th Annual port, 1980.
2. *Journal of Natural Products*, 42(2) March-[illegible]r 1980.
3. [illegible]*urnal of Pharmaceutical Sciences*, [illegible]1, 1971.
4. House Report 91-1444 (Part I), [illegible]prehensive Drug Abuse Prevention and [illegible]ol Act of 1970.
5. [illegible]/ashington Post, November 15, 1981, (F-[illegible]).
6. Institute of Medicine Report, pp. 25, 27, [illegible]41, and 43.
7. [illegible]IDA, Research Monograph Series No. [illegible]Marihuana Research Findings, 1980."
8. Addiction Research Foundation, 1981.
9. [illegible]*ournal of Clinical Pharmacology*, 21 (8 [illegible], Supplement), August-September 1981.
10. "Marihuana," ed. Raphael Mechoulam, [illegible]cademic Press, 1972.
11. "[illegible]harmacology of Marihuana," ed. [illegible]ra[illegible]nd Szara, Raven Press, 1976.
12. [illegible]tatement of William Pollin, M.D., [illegible]irector, National Institute on Drug Abuse, [illegible]efore the Committee on Foreign Affairs, [illegible]o[illegible]e of Representatives, April 20, 1982.
13. *American Journal of Drug and Alcohol* [illegible]b[illegible]e, 8(4), pp. 447-462, 1979.
14. NIDA, "Excerpts from the National [illegible]urvey on Drug Abuse—1979," U.S. Printing [illegible]f[illegible]e, 1980, O-311-248/6014.
15. [illegible]NIDA, Research Monograph Series No. [illegible]5, Demographic Trends and Drug Abuse [illegible]980-1995."
16. [illegible]*International Journal of the Addictions*, [illegible]S[illegible], pp. 304-321, 1980.
17. [illegible]Burt Associates, Inc., "Highlights from [illegible]he Worldwide Survey of Nonmedical Drug [illegible]Use and Alcohol Use Among Military [illegible]e[illegible]onnel, 1980," Contract No. NIDA 903-79-[illegible]>[illegible]67, Bethesda, MD.
18. Bulletin on Narcotics, XXXII, No. 4, pp. [illegible]39-45, 1980.
19. [illegible]. Bulletin on Narcotics, XXXIII, No. 1, pp. [illegible]1-[illegible], 1981.
20. [illegible]. Drug Enforcement Administration, *Drug Enforcement*, March 1980.
21. Project DAWN Annual Report—1980, [illegible]D[illegible]; Enforcement Administration and [illegible]N[illegible]onal Institute on Drug Abuse.
22. "Health Consequences of Marijuana [illegible]Use," Government Printing Office 869-675, [illegible]19[illegible].
23. [illegible]. AMA Council on Scientific Affairs, [illegible]"[illegible]rijuana in the '80s," Adopted by the [illegible]Hou[illegible]of Delegates, December 1980.

[illegible]ested persons may, on or before [illegible]O[illegible]ober 1, 1982, submit to the Dockets Management Branch (address above), written comments regarding this notice. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: June 7, 1982.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

[FR Doc. 82-17231 Filed 6-28-82; 8:45 am]

BILLING CODE 4160-01-M

Advisory Committees; Meeting

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: This notice announces a forthcoming meeting of public advisory committees of the Food and Drug Administration (FDA). This notice also sets forth a summary of the procedures governing committee meetings and methods by which interested persons may participate in open public hearings conducted by the committees and is issued under section 10(a)(1) and (2) of the Federal Advisory Committee Act (Pub. L. 92-463, 86 Stat. 770-776 (5 U.S.C. App. I)), and FDA regulations (21 CFR Part 14) relating to advisory committees. The following advisory committee meeting is announced:

Circulatory System Devices Panel

Date, time, and place. July 23, 8:30 a.m., Rm. 403-425A, 200 Independence Ave. SW., Washington, D.C.

Type of meeting and executive secretary. Open public hearing, 8:30 a.m. to 9:30 a.m.; open committee discussion, 9:30 a.m. to 10:30 a.m.; closed committee deliberations, 10:30 a.m. to 3:45 p.m.; open committee discussion 3:45 p.m. to 4:00 p.m.; Glenn A. Rahmoeller, Bureau of Medical Devices (HFK-450), Food and Drug Administration, 8757 Georgia Ave., Silver Spring, MD 20910, 301-427-7559.

General function of the committee. The committee reviews and evaluates available data on the safety and effectiveness of medical devices currently in use and makes recommendations for their regulation.

Agenda—Open public hearing. Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Those desiring to make formal presentations should notify the contact person before July 14, 1982, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time required to make their comments.

Open committee discussion. The committee will discuss several premarket applications (PMA's) for pacemakers and may also review one or more PMA's for other cardiovascular devices.

Closed committee deliberations. The committee may discuss trade secret or confidential commercial information relevant to one or more PMA's for pacemakers or other cardiovascular devices. This portion of the meeting will be closed to permit discussion of this information (5 U.S.C. 552b(c)(4)).

Each public advisory committee meeting listed above may have as many as four separable portions: (1) An open public hearing, (2) an open committee discussion, (3) a closed presentation of data, and (4) a closed committee deliberation. Every advisory committee meeting shall have an open public hearing portion. Whether or not it also includes any of the other three portions will depend upon the specific meeting involved. The dates and times reserved for the separate portions of each committee meeting are listed above.

The open public hearing portion of each meeting shall be at least 1 hour long unless public participation does not last that long. It is emphasized, however, that the 1 hour time limit for an open public hearing represents a minimum rather than a maximum time for public participation, and an open public hearing may last for whatever longer period the committee chairman determines will facilitate the committee's work.

Meetings of advisory committees shall be conducted, insofar as is practical, in accordance with the agenda published in this Federal Register notice. Changes in the agenda will be announced at the beginning of the open portion of a meeting.

Any interested person who wishes to be assured of the right to make an oral presentation at the open public hearing portion of a meeting shall inform the contact person listed above, either orally or in writing, prior to the meeting. Any person attending the hearing who does not in advance of the meeting request an opportunity to speak will be allowed to make an oral presentation at the hearing's conclusion, if time permits, at the chairman's discretion.

Persons interested in specific agenda items to be discussed in open session may ascertain from the contact person the approximate time of discussion.

A list of committee members and summary minutes of meetings may be

THE UNIVERSITY OF CHICAGO

DATE October 14, 1985

Frank Sapienza DEPARTMENT

FROM Lew Seiden DEPARTMENT

IN RE: MDMA Preliminary Results

Enclosed please find a corrected copy of my brief report on the preliminary results we have obtained with MDMA. As you can see, the last sentence in the second paragraph now refers to reuptake of serotonin instead of simply levels. Sorry for the error, and I hope it didn't cause problems for you. Should you require more information, give me a call.

October 4, 1985

Dr. Lewis S. Seiden
University of Chicago
Department of Pharmacological
and Physiological Sciences

REPORT OF PRELIMINARY RESULTS ON MDMA

We have treated rats with multiple or single injections of MDMA in varying doses to compare the neurotoxic consequences of MDMA with MDA. We have observed serotonin depletions in various parts of the brain, reduction in serotonin uptake, and positive Fink-Heimer stains in regions known to contain serotonin that showed serotonin depletions.

For the multiple injection experiments, MDMA was injected twice per day for 4 days at doses of 10, 20 and 40 mg/kg/injection. Two weeks after the last injection of MDMA, serotonin levels in the hippocampus, cortex, striatum, and hypothalamus, were depleted. This same pattern of depletion occurred after 8 weeks without drug. The most severe depletions were seen in the cortex and hippocampus 2 weeks after the drug where serotonin levels were depleted by more than 85%. Reuptake of serotonin in cortex was decreased by approximately 30%.

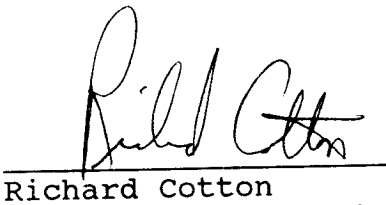
Examination of animals that have been treated with either acute or repeated doses of MDMA reveal mildly positive Fink-Heimer staining in the cortex after 1 injection, but after 8 injections, we observed positive Fink-Heimer stain in the cortex and striatum.

The decrease in uptake sites, the decrease in serotonin levels, and positive Fink-Heimer staining are indicative of neurotoxicity that is engendered by MDMA. These results are basically similar to results obtained with MDA with the exception of the fact that with MDA we saw more positive Fink-Heimers after 1 injection of MDA. However, MDMA shows a greater depletion of serotonin after repeated doses. We conclude from these results that a single injection of MDMA may not be as toxic as MDA but chronic treatment with MDMA appears at this point to be more toxic than MDA.

CERTIFICATE OF SERVICE

This is to certify that the undersigned on January 12, 1987 caused a copy of the foregoing to be mailed, postage paid, to the following:

Harry S. Harbin
Charlotte A. Johnson, Esq.
Narcotic and Dangerous, Drug Section
Criminal Division
U.S. Department of Justice
P.O. Box 521
Washington, D.C. 20044



Richard Cotton
Attorney for Petitioner