

CHAPTER 2

FROM PILOT DRUG TO THE PRESENT

ERA OF CAUTIOUS ACCEPTANCE (1989-1996)

The Transfer of Authority

On March 31, 1989, Dr. Carl Peck, Director of FDA's Center for Drug Evaluation and Research (CDER), announced that he was going to transfer authority for the review and approval of research involving Schedule I drugs, such as psychedelics and marijuana, away from the Division of Neuropharmacological Drug Products, directed by Dr. Paul Leber, to the newly established Pilot Drug Evaluation Staff (PDES), under the directorship of Dr. John Harter.⁴⁰⁴ Chapter 3 discusses the reasons for this transfer. At the time, psychedelic research in the United States had been almost completely blocked for more than two decades, with most research halted in 1965. Psychedelic research had not been made illegal by Federal law or by international treaty obligation. Rather, the FDA had made it virtually impossible for scientists to obtain permission to initiate psychedelic research and NIMH had withdrawn funding and sponsorship of such research.

As a result of internal FDA dynamics to be examined in detail in Chapter 3, the establishment of Pilot Drug led to the gradual transformation of the regulatory context for psychedelic and marijuana research. Policies put into place by Pilot Drug reversed decades of internal opposition to such research and enabled several scientists to begin FDA-approved clinical trials involving the administration of psychedelics and marijuana to human subjects.⁴⁰⁵

Reviewing The Past

In late 1989, Dr. Harter asked Dr. Curtis Wright, a Medical Review Officer working within Pilot Drug, to begin reviewing all protocols under the Division's purview that were on Clinical Hold.⁴⁰⁶ The goals of the review were to get a better understanding of Pilot Drug's new areas of responsibility, to assess the old IND applications, and to develop a strategy to reduce the backlog. The degree to which its backlog would be reduced was to be one of the primary measures by which Pilot Drug would be evaluated by senior FDA management.

⁴⁰⁴Staff. *Pink Sheet, Trade and Government Memos* April 3, 1989: 1.

⁴⁰⁵Dr. Harter died July 11, 1996. This author had several conversations with him from 1991-1994 but began researching this chapter after his death. The information to be presented about Dr. Harter comes in part from our few conversations, more so from his writings, and in large part from interviews conducted with his widow and other people who worked closely with him.

⁴⁰⁶personal communication, Dr. Wright, March 8, 1999. Dr. Wright is ex-Acting Director of Division of Anesthetics, Critical Care and Addiction Drug Products (DACCADP) and ex-Acting Director of PDES. He is currently working for industry.

According to Dr. Wright, “We went back through every single Investigative New Drug (IND) application that was still active, but on Clinical Hold. Every single one. And we started calling people. We found requests for hallucinogen research, marijuana research, LSD research, undercapitalized venture-capital drug products- all kinds of things- but many were put on hold and no one had figured out how to break them free.”⁴⁰⁷ In Dr. Wright’s view, the problem of backlogged Clinical Holds on psychedelic research protocols was caused by FDA. There were holds on projects seeking to study LSD, MDMA and DMT, with no clear information given as to how to address the issues on which the Clinical Holds were based. Dr. Wright reported that both he and Dr. Harter believed that “it is invidious to prevent research, even if it will produce results you don’t want.”⁴⁰⁸ Dr. Temple, FDA’s Associate Director for Medical Policy and Director, Office of Drug Evaluation I, claimed not to have been aware of the past difficulties psychedelic researchers had faced when their protocols went to Dr. Leber in Neuropharmacological Drug Products, only to be placed on a permanent Clinical Hold.⁴⁰⁹ According to Dr. Temple, these Clinical Holds had not been protested at his level.

Dr. Wright explained that Dr. Harter was open to the possibility that FDA might approve some psychedelic and marijuana research protocols. Dr. Wright noted that when Dr. Harter became the Director of Pilot Drug, he had a philosophical belief that, “If we could put a man on the moon, we could study any drug. The question is what precautions were needed to do so safely.”⁴¹⁰ According to Dr. Wright, whether a study can be conducted ethically is determined in large part by whether you can “give people [subjects] a fair and accurate assessment of the risks” of being a participant in the study.

Approving a Study

In 1990, in an historic turning point, Pilot Drug approved the first new psychedelic research protocol in about two decades. The protocol was submitted by Dr. Rick Strassman, University of New Mexico. Dr. Strassman’s efforts to obtain FDA permission to conduct psychedelic research had begun back in 1986, when he unsuccessfully submitted an MDMA research protocol to Neuropharmacological Drug Products. Giving up on MDMA research, Dr. Strassman had worked for almost two years to win approval for a DMT protocol. Dr. Strassman’s DMT experiment was designed as a Phase I dose-response double-blind safety study in which gradually increasing doses of the psychedelic drug DMT would be administered to human subjects.⁴¹¹ The first of 12 subjects were

⁴⁰⁷Dr. Curtis Wright interview in Pellerin C. *Trips: How Hallucinogens Work in Your Brain*. New York: Seven Stories Press, 1998: 163-164.

⁴⁰⁸personal communication, Dr. Wright, March 8, 1999.

⁴⁰⁹personal communication, Dr. Robert Temple, March 18, 1999.

⁴¹⁰personal communication, Dr. Wright, March 8, 1999.

⁴¹¹Strassman R. Human hallucinogenic drug research in the United States: a present-day case history and

treated in November 1990 and the last subject was treated in September 1991.⁴¹²

Pilot Drug also approved a NIDA-funded study in a single subject in which a low dose of LSD was administered in order to measure the detectability of the drug in human plasma.⁴¹³ In 1991, a new therapeutic study designed to evaluate LSD-assisted psychotherapy in the treatment of substance abusers was approved by Pilot Drug as part of Dr. Kurland's longstanding IND for LSD research.⁴¹⁴ Though approved, this study was never implemented due to lack of funding.⁴¹⁵

Pilot Drug's approval of three protocols involving the administration of DMT or LSD to human subjects occurred somewhat surprisingly at a time when the Drug War was still escalating. Even still, the social turmoil associated with psychedelics was rather muted by 1991. Crack cocaine had long since replaced LSD as the drug that generated the most fear in the public mind and the most headlines. In 1990 and 1991, Pilot Drug was able to approve protocols involving LSD and DMT with no apparent political outcry or bureaucratic cost. This suggests that while a major factor contributing to the cessation of psychedelic research in the late 1960s and early 1970s had been overwhelming external political pressure placed on FDA, the continued difficulties researchers faced over the course of the subsequent decades had more to do with the persistence of internal opposition to psychedelic research within FDA.

Federal Policies Governing Human Research

In 1991, a set of uniform regulations governing human research were codified for 16 federal agencies that conduct or sponsor research with human subjects.⁴¹⁶ These rules

review of the process. *J Psychoact Drug* 23 (1991) 1:29-38.

⁴¹²Strassman R. Human Hallucinogenic Drug Research: Regulatory, Clinical and Scientific Issues. in Lin G, Glennon R, (eds.) *Hallucinogens: An Update*. NIDA Research Monograph 146, Washington, DC, NIH Publication # 94-3872. 1994: 92-123.

⁴¹³Papac D, Foltz R. Measurement of lysergic acid diethylamide (LSD) in human plasma by gas chromatography/negative ion chemical ionization mass spectrometry. *J Anal Toxicol* 14 (May-Jun 1990) 3:189-90. The study took place at the Center for Human Toxicology, University of Utah, Salt Lake City.

⁴¹⁴IND #3052. The study was to be conducted by Dr. Kurland, Richard Yensen, Ph.D. and Dr. Donna Dryer, all in private practice. Revised protocol submitted to PDES by Dr. Kurland, January 22, 1991. Neither IRB approval nor a legal supply of FDA-approved LSD was in hand,, so the study could not begin despite FDA approval. Importation of LSD under DEA permit from U. of Berne, Switzerland took place in April 1996.

⁴¹⁵personal communication, Richard Yensen, May 1992.

⁴¹⁶Federal Policy for the Protection of Human Subjects, 56 FR 28003 (June 18, 1991). The FDA was not among the 16 Federal Agencies that joined in supporting the Common Rule. FDA announced its essentially similar regulations in the same edition of the Federal Register, 56 FR 28025, Food and Drug Administration, Protection of Human Subjects; Informed Consent; Standards for Institutional Review

apply to all research conducted or supported by any Federal agency and any research regulated by the FDA. These uniform regulations, known as the "Common Rule," established no entirely new regulatory mechanisms.⁴¹⁷ The regulations contained provisions concerning the composition, conduct and recordkeeping of IRBs,^{418 419} as well as policies regarding research involving fetuses, pregnant women, and human in vitro fertilization,⁴²⁰ prisoners,⁴²¹ and children.⁴²² The implementation of the Common Rules are overseen by NIH's Office for Protection from Research Risks (OPRR).

Compassionate Use of Marijuana

Pilot Drug received minimal internal or external criticism of its policies toward psychedelic research. Pilot Drug's policies toward the medical use of marijuana were another story and generated substantial controversy and pressure, both from external and internal sources.

In May 1978, over a decade prior to the establishment of Pilot Drug, NIDA and FDA had agreed in an out-of-court settlement⁴²³ to provide a legal supply of marijuana to Mr. Bob Randall, a glaucoma patient who was the first person to establish a claim of "medical necessity" for marijuana in a court of law.⁴²⁴ Over the next decade, Mr. Randall helped guide about a dozen patients into what became known as FDA's Compassionate IND program. This program provided marijuana grown by NIDA for free to a very small group of patients. Many of these patients had been involved in legal trouble surrounding their medical use of marijuana, all had physicians who had been willing to testify to their patient's medical necessity for marijuana. Though nominally supervised by the FDA, the

Boards for Clinical Investigations 21 CFR Parts 50 and 56.

⁴¹⁷ The Common Rule built on the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *Implementing Human Research Regulations*. Washington, DC: GPO, 1983. The Commission was established by the Community Mental Health Centers Act, Biomedical Research and Research Training Amendments of 1978, 95 P.L. 622; 92 Stat. 3420. Nov. 9, 1978.

⁴¹⁸⁴⁵ CFR 46. 107-119.

⁴¹⁹ For more information on Institutional Review Boards, see *Continued Vigilance Critical to Protecting Human Subjects*. General Accounting Office report to the Ranking Minority Member, Committee on Governmental Affairs, U.S. Senate. Washington, DC: 1996 and also *Institutional Review Boards: Their Role in Reviewing Approved Research*. Department of Health and Human Services, Office of the Inspector General, Washington, DC: 1998.

⁴²⁰⁴⁵ CFR 46.201-211. Subpart B.

⁴²¹⁴⁵ CFR 46.301-306. Subpart C.

⁴²²⁴⁵ CFR 46. 401-409. Subpart D.

⁴²³ Randall R. *Marijuana, Medicine and the Law*. Washington, DC: Galen Press, 1988: 39.

⁴²⁴United States v. Randall, 104 Daily Wash. L. Rep. 2249 (Super. Ct. D.C. Nov. 24, 1976).

few patients who received marijuana legally were not subjects in any formal research studies once they entered into the Compassionate IND program.

As the AIDS epidemic intensified during the 1980s, a growing number of AIDS patients began using marijuana to restore their appetites and reduce the nausea associated with their AIDS medications, in some cases with lifesaving effect for patients suffering from the AIDS wasting syndrome.⁴²⁵ In November 1989, Bob Randall advised Steve L. to become the first AIDS patient to submit an application to enter FDA's Compassionate IND program.⁴²⁶ Steve L. had been arrested for his use of marijuana while purchasing a small amount from an undercover narcotics agent.⁴²⁷ At the time Steve L. and his physician submitted the application to FDA, the Compassionate IND program was under the jurisdiction of Pilot Drug. Dr. Dan Spyker, Pilot Drug medical review officer, was assigned the responsibility of reviewing the applications to the program.⁴²⁸ Dr. Spyker approved Steve L.'s application and in January 1990 he received a legal supply of marijuana from NIDA. Steve L. remained in the Compassionate IND program a very short time, dying of AIDS only 18 days after receiving his first legal supply of marijuana.

In November 1990, Bob Randall assisted a second AIDS patient to apply for entrance into the Compassionate IND program. This patient was also approved by Dr. Spyker and received a legal supply of marijuana from NIDA.

On December 18, 1990, a fateful meeting took place at FDA between Bob Randall, his partner Alice O'Leary, his lawyer, Dr. Dan Spyker, Dr. Curtis Wright, and several other FDA officials.⁴²⁹ The meeting had been called by FDA in response to the increase in applications by patients for access to marijuana. During the meeting, Dr. Wright suggested to Bob Randall that he work to convert the applications to the Compassionate IND program into applications for a series of N=1 studies.⁴³⁰ These studies would gather data on each patient's responses to marijuana, alternative medications, and placebo, enabling the provision of marijuana to be part of a research process that might eventually generate sufficient data to enable Bob Randall to apply to have marijuana approved as a

⁴²⁵Randall R. *Marijuana and AIDS: Pot, Politics and PWAs in America*. Washington, DC: Galen Press, 1991.

⁴²⁶Appendix B, "AIDS Chronology," In Randall, R.C. *Marijuana and AIDS: Pot, Politics and PWAs in America*. Washington, DC: Galen Press. 1991: 148.

⁴²⁷Ibid., 5.

⁴²⁸personal communication, Dr. Dan Spyker, February 22, 1999.

⁴²⁹Randall B and O'Leary A. *Marijuana Rx—The Patients' Fight for Medicinal Pot*. New York: Thunder's Mouth Press, 1998: 351.

⁴³⁰A general model for N=1 studies has been described in the following paper: Larson E, Ellsworth A, Oas J. Randomized clinical trials in single patients during a 2-year period. *JAMA* 270 (1993 Dec 8) 22:2708-12. This paper was given to the author by Dr. Spyker as an excellent source of information about the purpose and design of N=1 studies.

prescription medicine.⁴³¹ As a further advantage of adopting the N=1 research approach, Dr. Wright indicated that the Compassionate IND program was vulnerable to being shut down. Bob Randall took Dr. Wright's comments as an FDA threat to shut down the Compassionate IND program.⁴³² He fundamentally failed to recognize the wisdom in Dr. Wright's suggestion that the best method of obtaining FDA approval for the medical use of marijuana would be to gather scientific data about marijuana whenever possible, just as would a pharmaceutical company seeking to obtain approval for any other drug. Bob Randall's decision not to work with FDA to facilitate N=1 studies in patients who could probably have been proven to benefit from marijuana's use was perhaps the key mistake made by proponents of the medical use of marijuana.

In February 1991, the third and fourth AIDS patients received their legal supplies of marijuana from NIDA as a result of their acceptance into the FDA's Compassionate IND program. Also in February 1991, Bob Randall formed the Marijuana AIDS/Research Service (MARS), an organization with a mission to assist AIDS patients in obtaining legal access to medical marijuana.⁴³³ Within the next several months, at least 40 more individuals applied for entrance into the Compassionate IND program.⁴³⁴ Dr. Spyker, with support from Dr. Harter, approved over twenty of these applications.⁴³⁵ Dr. Peck reported that complaints to FDA about Pilot Drug's approval of so many AIDS patients for entrance into the Compassionate IND came from the White House and upper management at HHS.⁴³⁶

The dramatic expansion of the Compassionate IND program placed an increasing demand on NIDA for additional supplies of marijuana. NIDA's situation was described by Dr. Cynthia McCormick, Director of FDA's Division Anesthetics, Critical Care and Addictive Drug Products (DACCADP). She reported "As I understand it, [this expansion] threatened the availability of marijuana for future single patient INDs and other research projects. In 1991, FDA sought assistance from the Department of Health and Human Services, Public Health Service, in dealing with the increasing number of single-patient INDs. This led to a review of the INDs by Assistant Secretary for Health [and Chief of the Public Health Service], Dr. James O. Mason."⁴³⁷

⁴³¹Ibid, 352.

⁴³²Ibid, 353.

⁴³³Randall R. (1991): 115.

⁴³⁴Kuromiya v. United States, 78 F. Supp. 2d 367 (E.D.Pa. 1999). Def. Ex. 1 ¶ 7; Def. Ex. 3 at 4; Def. Ex. 6 at 1, Plf. Ex. 2 at 30.

⁴³⁵Ibid.

⁴³⁶personal communication, Dr. Carl Peck, February 22, 1999.

⁴³⁷The quote from Dr. Cynthia McCormick, FDA's Division Director of Anesthetics, Critical Care and Addictive Drug Products (DACCADP), is from her testimony in a 1999 class action lawsuit that

On June 21, 1991, Dr. Mason announced that he was recommending that the Bush Administration shut down FDA's Compassionate IND program to new applicants while continuing to supply only those patients already receiving marijuana. Those patients who had been approved by FDA for entrance into the Compassionate IND program but had not yet received their first supplies would be dropped from the program. According to Dr. Mason, "If it's perceived that the Public Health Service is going around giving marijuana to folks, there would be a perception that this stuff can't be so bad. It gives a bad signal. I don't mind doing that if there's no other way of helping these people... But there's not a shred of evidence that smoking marijuana assists a person with AIDS."⁴³⁸ ⁴³⁹ As Dr. Mason indicated, the Compassionate IND program had generated no data about the medical use of marijuana in AIDS patients, pointing out the exactly the vulnerability of the Compassionate IND program that Dr. Wright had previously and unsuccessfully tried to point out to Bob Randall.

In a December 10, 1991 speech to the Food and Drug Law Institute, FDA Commissioner Dr. David Kessler didn't bother to mention the controversy Pilot Drug had generated over its approvals of Compassionate INDs and remained thoroughly supportive of Dr. Peck and Dr. Harter's management approach. Dr. Kessler remarked, "The current push to get important new therapies to patients sooner has captured the imagination of our Center for Drug Evaluation and Research. The number of pilot projects and creative ideas flowing out of that center has never been greater." In Dr. Peck's estimation, Dr. Kessler was somewhat aware and supportive of Pilot Drug, but wasn't deeply involved.⁴⁴⁰

On January 31, 1992, Dr. Mason wrote a memorandum to Dr. Louis Sullivan, Secretary of HHS, outlining his views on the Compassionate IND program for medical marijuana patients. Dr. Mason wrote that, "little or no useful data has been obtained...there

unsuccessfully attempted to force the Clinton Administration to accept more patients into the Compassionate IND program. Kuromiya v. United States, 78 F. Supp. 2d 367 (E.D.Pa. 1999). Def. Ex. 1 ¶ 7.

⁴³⁸Isikof M. HHS to Phase Out Marijuana Program; Officials Fear Sending 'Bad Signal' by Giving Drug to Seriously Ill. *The Washington Post*, June 22, 1991: A 14.

⁴³⁹The controversy surrounding the Compassionate Use program has not gone away. An 11/6/1999 editorial in the Washington Post urged the Clinton Administration to reopen the compassionate use program to terminally ill patients, stating, "Rather than harass doctors who prescribe marijuana, the administration should reopen the federal program under which, until 1991, marijuana was available to terminally ill patients." On December 1, 1999, a class action lawsuit attempting to force the reopening of the Compassionate Use program on equal protection grounds was dismissed.

1999 WL 1081059 (E.D.Pa.) Kiyoshi Kuromiya, et al., v. The United States of America. United States District Court, E.D. Pennsylvania. Civil Action No. 98-3439. Memorandum and Order, Katz, Senior Judge, December 1, 1999.

⁴⁴⁰personal communication, Dr. Peck, February 22, 1999. Dr. Peck is now Director of the Center for Drug Development Science, Georgetown University Medical Center.

is consensus within the Public Health Service that the single-patient IND process would not yield useful data in the future that would resolve the remaining safety and effectiveness issues." ⁴⁴¹ On March 4, 1992, Dr. Sullivan accepted Dr. Mason's recommendations and closed the program.⁴⁴² At the time the program stopped accepting new applicants in March 1992, there were thirteen participants.⁴⁴³

Dr Harter: Congressional Oversight

While Pilot Drug's expansion of the Compassionate Use program had met with opposition from senior Administration officials, Dr. Harter himself received some unwelcome personal attention from Congress for FDA's protracted approval process for Ansaid, an arthritis drug developed by Upjohn Co. for whose review he had been responsible prior to the establishment of Pilot Drug. On February 21, 1992, House Energy and Commerce Committee Chairman John Dingell (D-Mich.), whose committee had oversight responsibility for FDA matters, heard testimony from Dr. Harter about FDA's review of Ansaid. Cong. Dingell was upset that the New Drug Application (NDA) had been filed in 1982 but Upjohn had to wait six years for approval, which was finally granted in 1988. Cong. Dingell accused "people testifying today" [Dr. Harter] of "sloth, laziness, indifference and probably incompetence."⁴⁴⁴ Rep. Henry Waxman (D-Calif.), chairman of the Health and Environment Subcommittee that held the hearing, was not as critical of Dr. Harter. There is nothing in the record to indicate that the Compassionate IND program was mentioned during this hearing.

Pilot Drug and the Nicotine Patch

As part of its portfolio, Pilot Drug had the responsibility to regulate drugs for the treatment of addiction. As a result, the review of research into the use of nicotine patches for the treatment of addiction to cigarettes took place within Pilot Drug, with Dr. Spyker deeply involved in the process. Beginning in early 1992, Pilot Drug approved several nicotine patches, first Habitrol by Ciba-Geigy, then in short order Nicoderm by Marion Merrill Dow, Prostep by Lederle and Nicotrol by Warner Lambert. Within the first year, more than 200 million nicotine patches were sold for revenues in excess of \$1 billion.⁴⁴⁵

Pilot Drug's work on the nicotine patch soon led FDA Commissioner Dr. Kessler to work closely with Pilot Drug in his major attempt to assert FDA authority over the regulation of tobacco.

⁴⁴¹Kiyoshi Kuromiya, et al., v. The United States of America. Def. Ex. 3 at 4.

⁴⁴²Def. Ex. 4 at 27-28.

⁴⁴³.See Def. Ex. 1 ¶ 11. At the time of Dr. McCormick's testimony in 1999, eight patients remained in the program.

⁴⁴⁴Staff. *State News Service*, February 21, 1992.

⁴⁴⁵Barbour J. AP Newsfeatures, August 10, 1992.

Formal Clarification of Policies Toward Psychedelic Research by NIDA and FDA

In early 1992, Dr. Charles Grob, Harbor-UCLA, submitted a protocol to FDA designed to investigate the use of MDMA-assisted psychotherapy in terminal cancer patients.⁴⁴⁶ This was the first therapeutically-oriented protocol submitted to Pilot Drug. On July 15, 1992, in response to the gradually increasing interest among scientists in obtaining permission to conduct psychedelic research, Pilot Drug convened a meeting of its Drug Abuse Advisory Committee. The committee was charged with evaluating Pilot Drug's general policies regarding psychedelic research and was also asked to review Dr. Grob's specific protocol.⁴⁴⁷ In accordance with the Federal Advisory Committee Act of 1972,⁴⁴⁸ the FDA and other government agencies use expert advisory committees to provide guidance and advice on important matters coming before them. Though the FDA retains final authority to make decisions, the recommendations of its Advisory Committees are almost always accepted.

In order to help educate the Drug Abuse Advisory Committee, Dr. Wright asked NIDA if it would be willing to provide input to the Committee.⁴⁴⁹ In response to Dr. Wright's request, Dr. Geraline Lin, program officer in NIDA's Division of Basic Research, decided to convene a Technical Review of hallucinogens.⁴⁵⁰ Dr. Lin scheduled NIDA's Technical Review on July 14, 1992, the day before the Drug Abuse Advisory Committee meeting. NIDA had not convened a Technical Review of Hallucinogens in fourteen years, since 1978.⁴⁵¹

The consensus of the participants at both NIDA's Technical Review of Hallucinogens and FDA's Drug Abuse Advisory Committee was that human research with hallucinogens should be permitted. Since these meetings marked a historic turning point in formal federal policy toward psychedelic research in humans, the deliberations of the two groups concerning the appropriate policies toward psychedelic research will be thoroughly discussed. The methodological issues raised by the participants in these meetings will be addressed in greater detail in subsequent chapters.

No transcript is available for the NIDA meeting. However, a book was produced in

⁴⁴⁶IND #39,383.

⁴⁴⁷Transcript of the 23rd meeting of FDA's Drug Abuse Advisory Committee Meeting, July 14-15, 1992.

⁴⁴⁸Federal Advisory Committee Act of 1972. 92 P.L. 463; 86 Stat. 770. October 6, 1972.

⁴⁴⁹personal communication, Dr. Wright, March 8, 1999.

⁴⁵⁰NIDA's Technical Reviews usually involved a one or two day scientific meeting at which NIDA gathered together its research grantees along with some outside experts for a comprehensive review of the field under discussion. Technical Reviews usually result in a book that compiles the papers presented at the meeting.

⁴⁵¹Barnett G, Trsic M, Willette Robert E. (eds.) *QUASAR: Quantitative Structure-Activity Relationships of Analgesics, Narcotic Antagonists, and Hallucinogens*. NIDA Research Monograph 22. Washington, DC, NTIS PB# 292-265/AS. 1978.

NIDA's Research Monograph series that contains the papers presented by the conference participants.⁴⁵² There is a transcript for the open portion of FDA's meeting. The discussion about Dr. Grob's MDMA protocol took place during a closed session which was not recorded. FDA does not record closed sessions at which specific protocols are reviewed in order to protect the proprietary interests of pharmaceutical companies engaged in the competitive drug development business. This author was present at the NIDA meeting as an observer and at the FDA meeting as the sponsor of Dr. Grob's protocol.

NIDA Technical Review, July 13-14, 1992

Dr. Geraline Lin, the NIDA official who convened its review, described NIDA's agenda for the meeting, "Not only do we want to know what the current knowledge of hallucinogen drug research is, we also want to identify what our future research needs are in this area, both clinical and preclinical. We are also interested in exploring therapeutic utility, if there is any, for hallucinogenic drugs. Of course, we are interested in knowing chronic, long-term biological consequences of hallucinogenic use."⁴⁵³

In the opening talk of NIDA's Technical Review, Dr. Steven Szara, the retired chief of NIDA's Biomedical Research Branch, outlined the history of psychedelic research and identified six distinct eras which he defined by the predominant type of research that was conducted during that era. According to Dr. Szara, the first era from the early 1900s to the late 1940s, was the Hallucinogen Era, in which these drugs were considered to produce distortions of normal consciousness that provided users with a glimpse into the experiential world of the insane. The Psychotherapeutic Era, which lasted from the late 1940s to the early 1960s, developed in response to numerous reports that these drugs also produced experiences of profound insight, clarity, and deep emotionality that might have therapeutic potential. The Psychedelic Era, from the early to mid- 1960s, involved the increasing use by researchers of psychedelics in large doses with the aim of producing powerful, transcendent, cathartic experiences in a wide range of subjects such as ministers, prisoners, alcoholics, and terminal cancer patients. The Psychedelic Era also included an explosion of the non-medical use of psychedelics by young people in a counter-cultural movement linked to anti-war protests. The Behavioristic Era, in the late 1960s to the early 1970s, involved the use of psychedelics in animals by researchers seeking to understand the basic relationship between brain chemistry and behavior. The Era of Legal Limbo, from the early 1970s to the time of NIDA's 1992 Technical Review, involved the cessation of human studies, though some animal research continued.

According to Dr. Szara, the beginning of a new era, which he called Psychoheuristic, was underway. He coined the word "psychoheuristic" to indicate that

⁴⁵²Lin G, Glennon R (eds.). *Hallucinogens: An Update. NIDA Research Monograph 146*. Washington, DC, NIH Publication # 94-3872, 1994.

⁴⁵³Transcript of the Drug Abuse Advisory Committee. 23rd Meeting, Volume 11, Open Meeting, July 15, 1992: 15.

these drugs can be used as research tools to understand the workings of the human psyche. He intended the word "psychoheuristic" to focus attention on the context created by the people who administer the drug rather than on the drug itself. In this way, he tried to highlight the fundamental lesson learned from previous studies about the importance of the set and setting in shaping the remarkably wide range of experiences psychedelics can catalyze.⁴⁵⁴

The subsequent talks at NIDA's meeting primarily focused on the results of animal studies conducted by most of the researchers at the meeting. These presentations were about attempts to understand the functioning of the serotonin system and to develop methods of testing new compounds for psychoactivity.

A dramatic shift in emphasis took place during Dr. Alexander Shulgin's presentation. Dr. Shulgin reviewed the work he and his wife Ann conducted in which he synthesized hundreds of novel psychoactive compounds and tested them for activity on himself and a team of twelve research associates.⁴⁵⁵ Dr. Shulgin emphasized the incredible subtlety and unpredictability of the relationship between the structure of a compound and its psychoactivity. He cited instances where data from animal studies was contradicted by data from human reports and made an impassioned plea for more human studies. He referred to Dr. Szara's reference to the use of psychedelics to produce experiences of a religious, mystical nature and asked the assembled researchers and government officials to tell him how they would ever get rats to provide sufficient data on those matters. The response was, of course, laughter.

Dr. Shulgin's talk boldly discussed human experimentation outside of the context of FDA-approved clinical trials, with representatives of the DEA present in the room. This experimentation was arguably prohibited by a variety of regulations, most notably the requirement to conduct preclinical animal studies prior to introducing new compounds into humans, the requirement to obtain FDA approval prior to conducting human research, and the 1986 Controlled Substances Analogue Bill, which criminalized the administration to humans of novel substances that were similar in structure and effect to compounds that were already Scheduled.⁴⁵⁶ Dr. Shulgin's talk convinced the assembled scientists that he had carefully generated data of substantial importance. Dr. Shulgin's willingness to accept risks, both physical and legal, in order to advance scientific knowledge in this field helped to galvanize the participants to support the need for the resumption of FDA-approved human research. One subsequent speaker prefaced his talk on the effects of psychedelics in animals by acknowledging the courage of Dr. Shulgin in gathering human data, which he felt provided essential clues in interpreting the animal data.

⁴⁵⁴Szara S. Are Hallucinogens Psychoheuristic? *Hallucinogens: An Update*. Washington, DC. NIDA Monograph Series # 146. Washington, DC, NIH Publication #94-3872, (1994): 33-51.

⁴⁵⁵Shulgin S, Shulgin A. *PIHKAL:A Chemical Love Story*. Berkeley: Transform Press, 1991.

⁴⁵⁶Controlled Substances Analogue Enforcement Act of 1986. 99 P.L. 570. Oct. 27, 1986.

Dr. David Nichols, a NIDA-funded researcher at Purdue University who participated in the Technical Review, thought that the participants in the Technical Review would almost certainly have endorsed the resumption of human research even if Dr. Shulgin had not been in attendance.⁴⁵⁷ Dr. Nichols reported that there was already a widely perceived need among the scientists for more human data to help in the interpretation of their animal data.

At the conclusion of the Technical Review, Dr. Geraline Lin asked the group for a summary of their sense of the current state of research and of future directions to explore. In a subsequent interview, Dr. Lin described how a consensus had developed in favor of the resumption of clinical research in humans. She observed, “The problem is, [hallucinogen research on humans] has been banned for almost 30 years. But during that time we continued animal research and made tremendous progress in studying this class of drug in animals. The brain is complex, but compared to 30 years ago, we know so much more – about 5-HT and the 5-HT [family of] receptors and other systems. In the 1960s people just used LSD and described what happened. I don’t mean to say that that kind of information isn’t useful. But it’s also necessary to have scientific information, well-controlled and gathered by [scientific] investigators.”⁴⁵⁸

In his written statement, Dr. Szara wrote, “it is time...to recognize and emphasize the potentially immense heuristic value of these drugs in helping to explore the neurobiological bases of some fundamental psychic functions..hallucinogens should be viewed as powerful psychoheuristic tools that, in combination with other necessary conceptual (such as holarchic theory) and laboratory tools (such as PET scan or MRI), may help solve a major mystery of nature: the workings of human brains and minds.”⁴⁵⁹

In his written summary of the NIDA meeting, Dr. Richard Glennon, a NIDA-funded researcher who co-edited the book that emerged from the meeting, wrote “there was a consensus that there is an urgent need for new human testing...Legitimate human investigation with classical hallucinogens was severely curtailed about 25 years ago. During the ensuing period, a significant body of information has been accrued primarily on the basis of animal studies. Novel agents have been identified, mechanisms of action have been proposed, new animal models have been developed, and means to antagonize [block] the effects of classical hallucinogens have been described. New clinical data are now required to challenge or validate the results of these studies.”⁴⁶⁰

FDA Drug Abuse Advisory Committee 23rd Meeting, July 15, 1992

⁴⁵⁷personal communication, Dr. Nichols, June 20, 1999.

⁴⁵⁸Interview with Dr. Geraline Lin, in Pellerin C. *Trips: How Hallucinogens Work in Your Brain*. New York: Seven Stories Press, 1998: 169.

⁴⁵⁹Szara (1994): 47.

⁴⁶⁰Glennon R. Summary. Hallucinogens: An Update. *Hallucinogens: An Update*. NIDA Research Monograph 146. Washington, DC, NIH Publication # 94-3872, 1994: 300- 301.

Procedurally, the Committee was scheduled to meet in open session in the morning to discuss general policies toward psychedelic research and to review the scientific data about MDMA, particularly MDMA neurotoxicity. Government officials from NIDA, DEA, and the Office of National Drug Control Policy (ONDCP) were present at the open session as were TV and print reporters and members of the public. A portion of the open session was broadcast later that day on CNN.

The Advisory Committee was scheduled to go into closed session in the afternoon for the discussion of the specific MDMA protocol being reviewed. Scheduling the general discussion in the open session and reserving the discussion of specific protocols for closed sessions is the format preferred by pharmaceutical companies in order to protect against the disclosure of trade secrets such as protocol designs.⁴⁶¹ Reporters and members of the public were not allowed into the closed session. In addition to FDA officials and members of the Advisory Committee, the closed session included government officials from NIDA, DEA, the Office of National Drug Control Policy (ONDCP) and participants specifically invited either by Dr. Grob, the principal investigator of the proposed study, or by the organization that was the sponsor of Dr. Grob's protocol.⁴⁶² Though the non-profit organization that sponsored Dr. Grob's protocol lacked the resources of even a small pharmaceutical company, FDA treated the protocol application in the same way it would have treated an application from a major drug company.

FDA Drug Abuse Advisory Committee: Psychedelic Research in General

The open session portion of the meeting began with a review by Dr. Wright of the process that had led to the decision by FDA to convene its Drug Advisory Committee, Dr. Wright began by noting that "One of the first tasks which I took over was a review of all the protocols that had been placed on clinical hold. I can think of nothing that has a more chilling effect in research than to submit a protocol to a regulatory agency or an IRB and have it placed on hold and stay there a long time... It became clear to me that the Agency has a tremendous responsibility to take great care that the regulatory process does not become a major factor in the inhibition of needed research because it can easily do so."⁴⁶³

⁴⁶¹FDA regulations permit closed meetings for discussions of trade secrets, investigator files, sensitive internal documents, or matters involving personal privacy. 41 FR 52148 (November 26, 1976), 21 C.F.R. 14.25 and 14.27.

⁴⁶²To aid the Committee in its deliberations, the PDES arranged for six expert witnesses to address the committee in open session. These included MDMA neurotoxicity experts Dr. Lewis Seiden (U. of Chicago) and Dr. George Ricaurte (Johns Hopkins), senior clinical researchers Dr. Reese Jones (UCSF) and Dr. Murry Jarvik (UCLA), and Dr. Rick Strassman and Dr. David Nichols, both of whom were also at the NIDA meeting. Dr. Charles Grob was given an opportunity to address the Committee during the closed session concerning details of the MDMA protocol design.

⁴⁶³Transcript of the Drug Abuse Advisory Committee. 23rd Meeting, Volume 11, Open Meeting, July 15,

Dr. Wright next mentioned a core philosophy of Pilot Drug, stating, “The review division feels very strongly that it is possible to do research with most compounds provided we are able to define what the risks to the subjects are, and we are able to adequately monitor a research protocol so that the subjects that might become injured have such injury effect early, and at a stage where such injury, if it occurs, is reversible.”⁴⁶⁴

Dr. Wright announced that to prevent sham or fraudulent research with drugs with abuse potential, FDA required four minimal protocol design elements. These elements were, 1) a research hypothesis, 2) a defined size, 3) a defined duration, so that at a given point you will know if you have succeeded, failed, or had an indeterminate result, and 4) some kind of comparison group so that the hypothesis can be tested.⁴⁶⁵

Dr. Wright then outlined the primary risks he saw with psychedelic research. He told the Committee members that:

We believe that are special risks of neurological or psychological toxicity...there is the possibility for adverse events that occur with hallucinogens that may not be usual in the research environment...We are unclear as to how we should monitor for acute or long-term toxicity for these agents...We are not certain what the best subject population is for each kind of study in this area...there are some assumptions made about the chronically or terminally ill patients, they being a population that is suitable for certain kinds of studies. There are assumptions made about people who have elected to use these substances voluntarily in the past...We feel there is a real risk of premature widespread clinical use... We have a number of individuals who have already clearly expressed to us in written communications that they believe drugs of this class have been proven to be effective and they do not believe additional studies are needed. This raises the spectre that one or two poorly designed initial studies might result in widespread pressure for introduction of a therapy that is truly not effective. We have a problem chronically with drugs that produce unique or easily discriminated effects, and potential blindness in clinical trials is a problem.⁴⁶⁶

Dr. Wright concluded his opening statement by asking the committee to consider whether the standard FDA methods of evaluating drugs for safety and efficacy could be applied to psychedelics. He remarked, “These drugs are special but are they any more special than new cancer chemotherapy agents? Do they pose any more risk than other

1992: 6.

⁴⁶⁴Ibid., 7

⁴⁶⁵Ibid., 9.

⁴⁶⁶Ibid., 8-12.

neuropsychiatric agents? I think we need to deal with the issue of this class of drugs. I think we need to deal with it now.”⁴⁶⁷

The opening speaker was Dr. Geraline Lin. She spoke briefly about the consensus reached at NIDA’s Technical Review meeting in favor of renewed human research. She reported that the participants in the Technical Review “came to the conclusion that more research, both clinically and preclinically, is needed, especially on the clinical part. They feel that this is a badly needed area of research and everyone recognized that there is no substitute for human study. The final test is humans. But no one advocated that the studies should be uncontrolled and unlimited, but clinical, and objective and well-planned studies.”⁴⁶⁸

Dr. George Bigelow, a member of the Advisory Committee, asked Dr. Lin about the risk of neurotoxicity, inquiring, “I am just trying to get a feeling for the balance of the NIDA committee’s opinion about the relative risk of neurotoxicity. If the committee has recommended further clinical research, it sounds like their feeling is that while one needs to be concerned about it, it is not such a great concern that it should prevent research in this area.”⁴⁶⁹

Dr. Lin responded by noting, “the general feeling is that under well-controlled, well-planned conditions some limited clinical trials can be performed.”⁴⁷⁰

Dr. Reese Jones, who had been involved with psychedelic and marijuana research since the mid-1960s, had been asked by Pilot Drug to speak to the Advisory Committee about issues related to the conduct of clinical research with psychedelics. He began his presentation with a discussion of the political context for such research, remarking that:

One of the problems that plagues all of us who would like to do clinical studies with hallucinogens... is the burdens posed by the ghost of the past, not only Leary and the street use of hallucinogens and all the real problems that have been caused to both individual users and to society, but other, somewhat, now in retrospect, misguided, ill-guided experiments, done under medically controlled situations, done by CIA support, by the Army...Already this morning I have heard it said, as if it were a fact, that these are, as a class, a very toxic group, a very tricky, maybe hard to research group of substances, and I do not think they are. If you look at the literature from the late ‘50s and early ‘60s, the literature on clinical studies, laboratory studies, as a class these do not look like excessively dangerous, toxic drugs. Powerful drugs, yes. Fascinating

⁴⁶⁷Ibid., 12.

⁴⁶⁸Ibid., 17.

⁴⁶⁹Ibid., 19.

⁴⁷⁰Ibid., 19.

drugs, yes. But in terms of the general spectrum of behavioral toxicity, physiologic toxicity, if you look somewhat dispassionately at the numbers and the facts, they do not jump out at you as being all that different from other drugs that all of us have researched in the subsequent 25-30 years with reasonably acceptable risk and benefit ratios... The basic principles [for research studies] are laid out in the Helsinki principles.⁴⁷¹

Dr. Jones went on to highlight a risk he felt was likely to be greater in psychedelic psychotherapy research than in other psychiatric research, that being the question of obtaining truly informed consent in an uncoerced manner. Dr Jones elaborated:

Anybody who has done psychotherapy realizes that there is a great deal of power that one has, the control one has over one's patients. If it is a clinical trial on a new anti-depressant, even that is suspect. If one wants to approach a group of patients and say, "I'm your doctor. I think you're at a point in therapy where MDMA will assist you in the therapy,' can such a patient really give truly informed consent without coercion? I would argue probably not.

So, what is to be done? Well, it is not that difficult to allow someone else to handle the recruiting... There should at least be some attention and discussion of how to not abuse the privileges of the psychotherapist....I think if anything has changed in the last 25-30 years since the early '60s... it is a greater sensitivity to the issues of informed consent; knowledgeable participation; IRBs-- local human subject review really was in its infancy, or it did not even exist in the early '60s. And one should make the best use of that as a resource.⁴⁷²

Dr. Jones also made the Advisory Committee aware of a unique methodological challenge which FDA must address in psychedelic research projects. He offered that, "much of the research that I suspect a lot of us would like to see done is as much psychotherapy research as it is psychopharmacology research, and that is another sort of issue that I suppose presents new challenges to the FDA staff and to the Committee that do not come up as prominently as if we were looking at a new neuroleptic or a new antidepressant."⁴⁷³

Dr. Jones then urged the Committee and the FDA to be mindful of the political constraints that most likely would prevent researchers from obtaining federal funds for

⁴⁷¹Ibid., 31.

⁴⁷²Ibid., 33-34.

⁴⁷³Ibid., 35.

psychedelic research projects. He commented, “I would argue that in the beginning those who are reviewing protocols are going to have to make allowances for the fact that this is, to some extent, a boot-strap operation. I think to submit a perfectly designed, state-of-the-art protocol to NIDA on some hallucinogen-- I am not sure that it would be fundable just because the times are not really right for that.⁴⁷⁴ But the people who choose to be pioneers in this new venture are going to be doing it with limited resources. It is going to take a fair amount of judgement on the part of FDA staff and others who review the merits of the protocol, on what is the minimal protocol that protects the individual, the patient, and still will provide some useful data-- not what the ideal protocol is but what a minimal one is that we can live with.”⁴⁷⁵ In the context of compromises due to funding constraints, Dr. Jones raised the specific methodological issue of the appropriate length of time to administer outcome measures quantifying benefit as well as risk.

Dr. Jones concluded his presentation with an unequivocal endorsement of the resumption of human clinical research with psychedelics. He told the committee, “I encounter individuals who have had hallucinogenic therapeutic drug experiences 20 or 30 years ago, remember them vividly and say that it really made a difference in their lives. These are not controlled studies. It may be nothing more than something akin to a religious experience but who is to downplay the importance of religious experiences? If one contributes to it with a dose of MDMA, I think we should get on with it and try to see if there is a phenomenon there to study.”⁴⁷⁶

Another expert called by Pilot Drug to present information to the Committee was Dr. Rick Strassman, the only person who had at that time administered a psychedelic drug to human subjects under the auspices of an IND approved by Pilot Drug. Dr. Strassman discussed a paper that he had published reviewing reports of adverse effects in about 200 published articles involving the administration of psychedelics to human subjects.⁴⁷⁷ Dr. Strassman reported that he was persuaded by his review that clinical research with psychedelics could be conducted safely. He also reported that he had safely administered DMT to human subjects in the context of his own clinical research. Dr. Strassman told the Committee that psychedelic researchers should be required to have special training, specifically “in terms of interacting with quite regressed people. Individuals on these drugs

⁴⁷⁴Ironically, in 1996, Dr. Jones was part of a scientific review body convened by NIDA’s Medication Development Division that decided to recommend that NIDA not to fund human clinical research into the use of a psychedelic drug, ibogaine, for the treatment of heroin addicts going through withdrawal. Though this decision was ascribed primarily to concerns over safety, FDA, specifically PDES, approved the protocol and decided that the risk/benefit ratio was favorable. This is discussed a bit later in the dissertation.

⁴⁷⁵Transcript of the Drug Abuse Advisory Committee. 23rd Meeting, Volume 11:36.

⁴⁷⁶Ibid., 41.

⁴⁷⁷Strassman R. Adverse reactions to psychedelic drugs: A review of the literature. *J Nerv Ment Dis* 172 (1984) 10:577-95.

are quite regressed. So I think one's clinical experience is important in being able to manage these sorts of regressed states...A trained clinician needs to be the one responsible for giving these drugs.”⁴⁷⁸ In regard to the study of adverse neurological effects, Dr. Strassman expressed the opinion that prospective data from controlled clinical trials was necessary and that it was not sufficient to study non-medical users of psychedelics who took drugs of uncertain purity in uncontrolled environments with unknown preconditions or predisposing factors.⁴⁷⁹

Dr. Wright then emphasized to the Committee that standardized criteria for evaluating research protocols could help ensure that psychedelic research would be conducted safely, Dr. Wright summarized the steps that Dr. Strassman took in terms of preparing for his study, steps that contributed to a study that was implemented without significant adverse outcomes. Dr. Wright listed these elements as 1) conducted prior review of animal and clinical literature, 2) interviewed users to determine likely effects and possible adverse events, 3) defined pharmacologic and safety outcomes, 4) prepared for likely adverse events, 5) defined stopping rules for the clinical investigation, 6) proceeded step-wise in dosing, and 7) followed up patients for a substantial amount of time. Dr. Strassman added one additional step: spending a “fair quantity of time talking to these people [subjects] about what they might possibly expect and what sorts of things might occur in the worst of circumstances and the best of circumstances.”⁴⁸⁰

Up to this point in the open session, Dr. Harter had remained silent and had let Dr. Wright conduct the entire meeting. Dr. Harter decided to comment on a methodological issue raised by Dr. Jones, that of obtaining informed consent. Dr. Harter noted that having a colleague recruit subjects could give a false sense of objectivity, since everyone has some degree of bias. Dr. Harter suggested that perhaps an investigator who knew the most about the study and was sensitive to the issue of coercion might be the person best able to recruit subjects. Dr. Jones clarified his prior statement as applying only to the special case of the recruitment into a study by therapists of patients with whom they already have an ongoing long-term therapeutic relationship. Dr. Harter then wondered if the Institutional Review Board (IRB) might play a helpful role, but both Dr. Jones and Dr. Strassman thought that in this special case, psychiatric colleagues would be best qualified to review the discussion with a patient over his or her participation in a study. Dr. Wright concluded that this was an important matter of concern and that FDA needed to ensure that attention was paid to this issue in any psychotherapy protocols.⁴⁸¹

After a series of discussions about MDMA neurotoxicity, Dr. Wright sought to determine if a consensus had emerged during the open session regarding the issue of research with psychedelic drugs in general. He summarized:

⁴⁷⁸Transcript of the Drug Abuse Advisory Committee. 23rd Meeting, Volume 11:51, 58.

⁴⁷⁹Ibid., 59.

⁴⁸⁰Ibid., 52.

⁴⁸¹Ibid., 57.

I have not heard so far this morning any discussion of risks involving the use of these compounds that we do not routinely face with every new drug that we put through the IND process. We have a variety of agents that cause permanent lasting change in individuals that we have already in therapeutic use and continue to approve. I have heard great concern expressed this morning by almost every speaker that the usual standards of research must be followed; that there must be meticulous attention to the questions of patient selection, informed consent, monitoring at the edge of our abilities... I have heard that there is concern. I have heard that there is risk. I have heard that there is emotional and political sensitivity in this area. But I have not heard anything that leads me to believe that this is a qualitatively different kind of research than the rest of research that we do with other agents, especially agents that act on the brain... I would like to know what the Committee thinks.⁴⁸²

The Acting Chair of the Committee, Dr. Richard Meisch, responded, “Speaking for myself, I agree with your assessment.”⁴⁸³ No other members of the Committee responded to Dr. Wright’s request for their opinion, and the open portion of the meeting concluded.

FDA Drug Abuse Advisory Committee and the MDMA Research Protocol

In regard to the specific protocol at issue, Dr. Wright began the closed portion of the meeting by presenting to the Advisory Committee members a written review of FDA responses to all previous INDs requesting permission to administer MDMA to human subjects.⁴⁸⁴ All INDs had been placed on Clinical Hold due to concerns over neurotoxicity. In one instance, FDA rejected a request to conduct a single patient case study in a terminal cancer patient who had previously been administered MDMA-assisted psychotherapy when MDMA was legal, and had found it to be helpful. Dr Wright had written about FDA’s decision to place that IND on Clinical Hold, saying, “Ethically, not supplying a drug which has been found to be subjectively helpful to a pre-terminal cancer patient on the basis of possible future toxicity, is hard to justify.”⁴⁸⁵

The ensuing discussion of the cancer patient protocol focused in large part on the evidence for MDMA neurotoxicity that had been presented in the open session. Dr. George

⁴⁸²Ibid., 77-78.

⁴⁸³Ibid., 78.

⁴⁸⁴This discussion was part of the closed session of the Advisory Committee meeting and as such was not recorded. This author was present at the meeting and, in the absence of a transcript, has described the exchange from memory.

⁴⁸⁵Dr. Curtis Wright, author of background material attached to Zwanzier L. Executive Secretary, FDA Drug Abuse Advisory Committee. Letter to Dr. Charles Grob. June 26, 1992.

Ricaurte, the leading NIDA-funded U.S. researcher on MDMA neurotoxicity, had made a presentation about MDMA neurotoxicity, in terms of preclinical screening and clinical monitoring. He pointed out that extrapolating to humans from animal data depended upon species, dose amount, dosing schedule, route of administration, and age of the test animals. He commented that the definition of neurotoxicity was fluid and could require either a long-lasting chemical change, the addition of a morphological change associated with the chemical change, an actual functional consequence, or even the requirement that the changes be permanent and not reversible.⁴⁸⁶ ⁴⁸⁷

Dr. Strassman commented that he found that of his subjects in the DMT study, 6 had taken MDMA more than 10 times and 5 had taken it one time or not at all. When he compared the responses of the two different groups, he could find no differences in a variety of physiological measures, some of which were mediated by serotonin, between the 10X MDMA group and the 1X or no-use MDMA group.⁴⁸⁸ He concluded that in his limited sample, there was no evidence that MDMA had caused any permanent changes in the subjects who had taken MDMA more than 10 times.

Dr. Jones had raised the issue of the claims in the late 1960s of LSD-caused chromosome damage. These claims generated a great deal of fear, helped bring an end to LSD research, but later proved to be without clinical significance.⁴⁸⁹ Dr. Jones pressed Dr. Ricaurte to report what functional consequences had been found in animal studies and to suggest what outcome measures should be used in clinical trials to monitor for functional consequences. Dr. Ricaurte replied that the functional role of serotonin was not well understood, that functional consequences had not yet been identified and that any changes were likely to be subtle. He remarked that perhaps functional consequences might develop over time as the person or animal ages.⁴⁹⁰

⁴⁸⁶Transcript of the Drug Abuse Advisory Committee. 23rd Meeting, Volume 11:59-70.

⁴⁸⁷For information on Dr. Ricaurte's MDMA neurotoxicity research, see McCann U, Szabo Z, Scheffel U, Dannals R, Ricaurte G. Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings. *Lancet* 352 (1998): 1433-37; Hatzidimitriou G, McCann U, Ricaurte G. Altered serotonin innervation patterns in the forebrain of monkeys treated with MDMA seven years previously: Factors influencing abnormal recovery. *J Neurosci* 19 (1999) 12:5096-5107; Bolla K, McCann U, Ricaurte G. Memory impairment in abstinent MDMA ("ecstasy") users. *Neurology* 51 (1998): 1532-1537; McCann U, Mertl M, Eligulashvili V, Ricaurte G. Cognitive performance in (\pm) 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") users: a controlled study. *Psychopharmacology* 143 (1999): 417-425.

⁴⁸⁸Transcript of the Drug Abuse Advisory Committee. 23rd Meeting, Volume 11:71.

⁴⁸⁹For a review of the scientific literature on LSD and chromosome damage, see Grof S. Appendix 2: The Effects of LSD on Chromosomes, Genetic Mutation, Fetal Development and Malignancy. *LSD Psychotherapy*. Pomona, CA: Hunter House, 1980: 318-347.

⁴⁹⁰Transcript of the Drug Abuse Advisory Committee. 23rd Meeting, Volume 11:71-73.

In the closed session, Dr. Wright asked Dr. Ricaurte to estimate the neurotoxic risk to subjects in Dr. Grob's proposed experiment with MDMA. After considered reflection, Dr. Ricaurte stated that the doses called for in the experiment would not likely pose a large risk of serious functional consequences to the subjects, either to cancer patients or healthy normals.⁴⁹¹ This exchange between Dr. Jones and Dr. Ricaurte was the most important of the closed session. As a result of Dr. Jones' forceful questioning, Dr. Ricaurte reluctantly offered a reasonable risk analysis, which seemed to guarantee that Dr. Grob would be permitted to go forward in some manner or another.

The Committee then discussed various aspects of the protocol and suggested several changes. Dr. Wright suggested that the Committee not get bogged down in details, which the FDA staff could better handle at a later time, but should consider the two basic questions posed during the open session. First, should human studies with MDMA and other psychedelics be conducted? And if so, was psychedelic research sufficiently unique such that a new set of standards and procedures needed to be created to evaluate the studies?

The Committee decided that the benefits of gathering scientific information about MDMA and other hallucinogens through the use of human studies warranted the risks to subjects and society of conducting such research. The Committee also felt that research into the medical uses of "hallucinogens" was most appropriately regulated in the same manner and held to the same rigorous scientific standards for safety and efficacy as medical research with any other drug that the FDA would be asked to review.

The protocol was then examined in the light of the developing consensus that psychedelic research should be evaluated just like research with any other drug reviewed by FDA. In this context, it was seen as unusual for the first FDA-approved human study of a drug to begin with an investigation of therapeutic utility, since the standard procedure would be first to conduct a basic Phase I dose-response safety study in healthy volunteers. Though MDMA had been used therapeutically in cancer patients prior to its placement in Schedule I in 1985, that use had not been conducted in a research context and had not generated the kind of safety data that FDA was used to evaluating prior to the initiation of studies in a patient population. The recommendation of the Advisory Committee was that Pilot Drug work with Dr. Grob to develop designs for a Phase I safety study and for a study in cancer patients, with the cancer patient study postponed until after the completion of a Phase I study in healthy volunteers. The Advisory Committee further recommended that the Phase I study enroll only subjects who had already self-administered MDMA and had thereby demonstrated a willingness to accept the risks of potential MDMA neurotoxicity. This inclusion criteria introduced an intentional selection bias in favor of subjects who felt comfortable with the MDMA experience. As a result, these subjects were likely to be able to undergo the invasive nature of the testing procedures with minimal discomfort or adverse psychological reactions. Unfortunately, this selection bias would

⁴⁹¹This interchange took place during the closed session, in which no transcript or recording was made.

make it more difficult to generalize the results of this study to subjects who had no prior experience with MDMA, such as potential patients. Nevertheless, prior to Pilot Drug, FDA's Division of Neuropharmacological Drug Products had not applied a balanced risk/benefit analysis to its review of MDMA research protocols. Given the potentially devastating impact on the entire program of research if one subject were to experience a serious adverse effect during the course of the study, FDA, the Drug Abuse Advisory Committee and Dr. Grob all agreed that the added margin of safety for this initial Phase I study was worth the tradeoff.

Pilot Drug's New Policy

From Pilot Drug's bureaucratic perspective, the Advisory Committee's recommendation that psychedelic research be regulated like any other drug was an excellent outcome. Pilot Drug and FDA retained the maximum amount of authority and independence in reviewing psychedelic research protocols. No additional oversight or approval on matters of protocol design would be necessary from DEA or ONDCP. This wouldn't be an advantage if oversight would likely be helpful. However, DEA oversight of research with scheduled drugs being tested for use in the treatment of addiction has been strongly criticized as counter-productive by an Institute of Medicine study that will be discussed shortly.⁴⁹²

Pilot Drug's independence in reviewing psychedelic research protocols did come with a cost. Pilot Drug had to assume greater responsibility for the outcome of the studies it approved. There would be no other agencies or groups to blame if serious mishaps were to develop. Pilot Drug could also justifiably take a larger share of the credit if the studies went well.

In contrast to Pilot Drug's relative autonomy in regard to developing the field of psychedelic research, current HHS regulations for medical marijuana research require a separate PHS/NIDA review committee to approve all FDA-approved protocols before NIDA will agree to sell at cost the marijuana needed for a study that only it can legally provide.⁴⁹³ This has substantially slowed efforts to conduct medical marijuana research.

⁴⁹²Fulco C, Liverman C, Earley L (eds.) *Development of Medications for the Treatment of Opiate and Cocaine Addictions: Issues for the Government and Private Sector*. Washington, DC: Institute of Medicine, National Academy Press, 1994.

⁴⁹³In the case of psychedelics, there are numerous manufacturers/suppliers other than NIDA with the necessary licenses from DEA and the capability to produce psychedelics of sufficient purity to be acceptable to FDA for use in clinical research. As a result, NIDA supplies of psychedelics are not necessary for FDA-approved research to proceed, leaving NIDA with no authority over FDA-approved psychedelic research protocols. In contrast, the only facility in the United States with a DEA license to grow marijuana for research, located at the University of Mississippi, grows all of its crop under contract to NIDA and will not produce any for other purchasers.

Prescription Drug User Fee Act of 1992

On October 29, 1992, Congress passed the Prescription Drug User Fee Act of 1992.⁴⁹⁴ This Act mandated the payment by pharmaceutical companies of fees for having drugs reviewed for new drug approval by FDA, for supplemental approvals for drugs that were already prescription drugs,⁴⁹⁵ for having prescription drugs already on the market,⁴⁹⁶ and for having a manufacturing establishment.⁴⁹⁷ There are no fees for the review of INDs. The increased contribution to FDA's budget was intended to enable it to increase staffing levels substantially, with the corresponding expectation that NDA review times would decrease substantially. The Act contained a sunset provision of five years, in order to keep FDA focused on reaching the goals for the timely review of submissions that the extra staff was supposed to enable FDA to accomplish.⁴⁹⁸ The significance of this Act for Pilot Drug and for psychedelic and medical marijuana research will be discussed in Chapter 3.

International Narcotic Control Act of 1992

On November 2, 1992, just days before the Presidential election, Congress passed the International Narcotics Control Act, ratifying the United Nations Convention Against Illicit Traffic in Narcotic Drugs.⁴⁹⁹ The Convention had been adopted on December 19, 1988, at the 6th plenary meeting of the Nations who were parties to the 1962 Single Convention and the 1971 Convention on Psychotropic Substances.⁵⁰⁰ True to the pattern established by the United States Congress in regard to the first two major international drug control conventions, several years went by before the treaty was ratified by the United States.

Neither the Convention Against Illicit Traffic in Narcotic Drugs nor the International Narcotic Control Act of 1992 criminalized any new class of drugs or created any entirely new set of regulations. No new regulations impacting on medical research or possible prescription use of Schedule I drugs were proposed. The Convention and the Act both focused on fostering closer international cooperation in the effort to reduce the flow of illicit drugs across international borders and on facilitating the arrest and disruption of international criminal organizations engaged in the drug trade.⁵⁰¹

⁴⁹⁴Prescription Drug User Fee Act of 1992. 102 P.L. 571; 106 Stat. 4491. October 29, 1992.

⁴⁹⁵Sec. 736 (a) (1) The fee was initially set at \$100,000 per New Drug Application (NDA) and \$50,000 per Amended New Drug Application (ANDA), also known as a Supplemental New Drug Application.

⁴⁹⁶Sec. 736 (a) (3). The fee was initially set at \$6,000 per product on the market.

⁴⁹⁷Sec. 736 (a) (2). The fee was initially set at \$60,000 per facility.

⁴⁹⁸Sec. 105. "The amendments made by section 103 shall not be in effect after October 1, 1997."

⁴⁹⁹International Narcotics Control Act of 1992. 102 P.L. 583; 106 Stat. 4914. November 2, 1992.

⁵⁰⁰The treaty was ratified in Vienna, where the International Narcotic Control Board is located.

⁵⁰¹The 1992 Act was Amended in 1994. International Narcotics Control Corrections Act of 1994. 103

German Psychedelic Research Moves Forward

In 1992, several research papers from a new psychedelic research team in Germany were published. A basic Phase I study under the direction of Dr. Leo Hermle and Dr. Manfred Spitzer involved the administration of mescaline to 12 subjects.^{502 503} The research began in the Department of Psychiatry, Christophsbad, in Göppingen and expanded to include studies with MDE.⁵⁰⁴ Psilocybin research also took place at the Psychiatrische Universitätsklinik, Heidelberg.⁵⁰⁵ Basic Phase I studies with MDE, under the direction of Dr Hermle and Dr. Efi Gouzoulis, took place at the University of Freiburg.^{506 507 508} Research continued at the University of Technology (RWTH), Aachen.^{509 510 511 512}

P.L. 447; 108 Stat. 4691 NATO Participation Act of 1994 (Title II at 108 Stat 4695) November 2, 1994.

⁵⁰²Hermle L, Funfgeld M, Oepen G, Botsch H, Borchardt D, Gouzoulis E, Fehrenbach R, Spitzer M. Mescaline-induced psychopathological, neuropsychological, and neurometabolic effects in normal subjects: experimental psychosis as a tool for psychiatric research. *Biol Psychiat* 32 (Dec. 1, 1992) 11:976-91.

⁵⁰³Hermle L, Gouzoulis-Mayfrank E, Spitzer M. Blood flow and cerebral laterality in the mescaline model of psychosis. *Pharmacopsychiatry* 31 (Jul 1998) Suppl 2:85-91.

⁵⁰⁴Hermle L, Spitzer M, Borchardt D, Kovar K, Gouzoulis E. Psychological effects of MDE in normal subjects. Are entactogens a new class of psychoactive agents? *Neuropsychopharm* 8 (Feb 1993) 2:171-6.

⁵⁰⁵Spitzer M, Thimm M, Hermle L, Holzmann P, Kovar K, Heimann H, Gouzoulis-Mayfrank E, Kischka U, Schneider F. Increased activation of indirect semantic associations under psilocybin. *Biol Psychiatry* 39 (Jun 1996) 12:1055-7.

⁵⁰⁶Gouzoulis E, Steiger A, Ensslin M, Kovar A, Hermle L. Sleep EEG effects of 3,4-methylenedioxymethamphetamine (MDE; "eve") in healthy volunteers. *Biol Psychiat* 32 (December 15, 1992) 12:1108-17.

⁵⁰⁷Gouzoulis E, Borchardt D, Hermle L. A case of toxic psychosis induced by 'eve' (3,4-methylene-dioxyethylamphetamines). *Arch Gen Psychiat* 50 (Jan 1993) 1:75.

⁵⁰⁸Gouzoulis E, von Bardeleben U, Rupp A, Kovar KA, Hermle L. Neuroendocrine and cardiovascular effects of MDE in healthy volunteers. *Neuropsychopharm* 8 (May 1993) 3:187-93.

⁵⁰⁹Gouzoulis-Mayfrank E, Heekeren K, Thelen B, Lindenblatt H, Kovar K, Sass H, Geyer M. Effects of the hallucinogen psilocybin on habituation and prepulse inhibition of the startle reflex in humans. *Behav Pharmacol* 9 (Nov. 1998) 7:561-6.

⁵¹⁰Gouzoulis-Mayfrank E, Thelen B, Habermeyer E, Kunert H, Kovar K, Lindenblatt H, Hermle L, Spitzer M, Sass H. Psychopathological, neuroendocrine and autonomic effects of 3,4-methylenedioxymethamphetamine (MDE), psilocybin and d-methamphetamine in healthy volunteers. Results of an experimental double-blind placebo-controlled study. *Psychopharm (Berl)* 142 (Feb 1999) 1:41-50.

⁵¹¹Gouzoulis-Mayfrank E, Schreckenberger M, Sabri O, Arning C, Thelen B, Spitzer M, Kovar KA,

The basic conceptual approach is that of “model psychosis,” which characterizes the psychedelic state as similar to psychosis. No therapy studies were conducted. Unlike in Switzerland, the research in Germany continued without interruption through the 1990s, perhaps because the researchers were careful to keep within a slightly pejorative framework and didn’t press to conduct therapy studies.

United States Research Slowly Expands

Dr. Grob’s revised protocol for a Phase I MDMA safety study was subsequently approved by Pilot Drug in early November 1992.⁵¹³ Subjects were indeed required to have had prior exposure to MDMA. In 1993, FDA gave approval to Dr. Sanchez-Ramos and Deborah Mash, Ph.D. for a Phase I ibogaine dose-response study.⁵¹⁴ These subjects were also required to have prior experience with ibogaine, and to have had a history of substance abuse that was in remission at the time of the experiment. The FDA subsequently modified the study to open it to persons with no prior ibogaine experience.

Pilot Drug Approves LAAM

In April 1993, FDA approved LAAM, a long-lasting methadone for the treatment of addiction. LAAM had been in development for over a decade and had become stalled in Neuropharmacological Drug Products. It was then revived in 1990 by Pilot Drug and NIDA’s Medications Development Division (MDD).⁵¹⁵ The amount of time from NIDA’s submission to FDA of its NDA for LAAM to FDA approval was only 18 days, the shortest NDA review time in FDA’s history. Pilot Drug had worked extremely closely with MDD in the design of new clinical trials and in their analysis, providing a highly visible example of Pilot Drug’s experimental interactive approach that will be discussed further in Chapter

Hermle L, Bull U, Sass H. Neurometabolic effects of psilocybin, 3,4-methylenedioxymethamphetamine (MDMA) and d-methamphetamine in healthy volunteers. A double-blind, placebo-controlled PET study with [18F]FDG. *Neuropsychopharmacology* 12 (Jun 1999) 6:565-81.

⁵¹²Schreckenberger M, Gouzoulis-Mayfrank E, Sabri O, Arning C, Zimny M, Zeggel T, Wagenknecht G, Kaiser HJ, Sass H, Buell U. "Ecstasy"-induced changes of cerebral glucose metabolism and their correlation to acute psychopathology. An 18-FDG PET study. *Eur J Nucl Med* 26 (Dec. 1999) 12:1572-9.

⁵¹³Approved November 5, 1992. IND #39,383. A Phase 1 dose- response safety study conducted by Dr. Charles Grob, Harbor UCLA.

⁵¹⁴August 25, 1993. FDA Drug Abuse Advisory Committee meeting recommended approving the Phase 1 dose- response safety study proposed by Dr. Juan Sanchez-Ramos and Deborah Mash, Ph.D., U. of Miami Medical School. The Advisory Committee recommended the approval of three dose levels, 1 mg/kg, 2 mg/kg and 5 mg/kg, with prior approval by FDA required before each dose escalation. The Advisory Committee also recommended that only subjects who had previously tried ibogaine be allowed to participate in the study.

⁵¹⁵Grudzinskas C, Wright C. An 18-day Approval Becomes Reality. *Pharma Executive* 10 (October 14, 1994): 74-80.

3.

Swiss Research Rapidly Contracts

In 1993, the Swiss Ministry of Health withdrew permission from the entire small group of Swiss psychiatrists who had been able to administer MDMA and LSD to their patients. The Ministry was reacting to the ibogaine-related death of a patient of one of the Swiss psychiatrists during a group workshop that was held in France, where the psychiatrist was not licensed and used a drug that he was not authorized to administer. The Ministry was also disappointed to learn that the Swiss psychiatrists had not conducted any research during the 5 years they had permission to work with LSD and MDMA, but had focused their efforts simply on treating their patients.⁵¹⁶

The Swiss Ministry's decision to withdraw permission to use MDMA and LSD from all Swiss psychiatrists as a result of a single tragic adverse effect from a different drug demonstrates the sensitive nature of this research. Seen in this light, it is easier to understand the rationale for the selection bias FDA imposed on the design of Dr. Grob's MDMA Phase I study as a result of its insistence on enrolling only subjects with prior exposure to MDMA.

Dr. Peck and Dr. Harter Retire

On November 1, 1993, Dr. Peck retired. Within a month or so, Dr. Harter retired. Dr. Wright became Acting Director of Pilot Drug around February 1994. Around this same time, Dr. Spyker transferred out of Pilot Drug to the Center for Devices and Radiological Health. In January 1994, Dr. Janet Woodcock's appointment as the new Director of CDER was announced. HHS cleared her appointment in mid-May 1994.⁵¹⁷ The factors that led to these management changes and the implications for Pilot Drug and for psychedelic and medical marijuana research will be discussed in Chapter 3.

Pilot Drug's Policies Endorsed by New Leadership

On May 16, 1994, Pilot Drug, with Dr. Wright as Acting Director, expressed a willingness to approve a NIDA/MDD-proposed placebo-controlled study of ibogaine in persons having substance-related disorders, if NIDA decided to go ahead with the protocol.⁵¹⁸ On August 1994, Pilot Drug approved Dr. Rick Strassman's application to conduct a Phase I dose-response psilocybin study.⁵¹⁹

According to Dr. Wright, " [In late 1994 or early 1995], the Deputy Center

⁵¹⁶personal communication, Dr. Peter Gasser, November 1993.

⁵¹⁷Staff. The Woodcock Era Begins at CDER. *US Reg Repor*10 (May 1994) 11:1.

⁵¹⁸May 16, 1994. NIDA Second Ibogaine Protocol Design meeting.

⁵¹⁹Approved August 10, 1994. IND #39258. A Phase 1 dose- response safety study conducted by Dr. Rick Strassman, U. of New Mexico Medical School.

Director [Mr. Gerald Meyer] wrote a very nice statement. It said basically that we were going to treat [hallucinogens, marijuana and other drugs of abuse] no differently than any other [drug]. That's what the Advisory Committee recommended and that's what we've done ever since.”⁵²⁰

Pilot Drug and Tobacco Regulation

Due to the expertise Pilot Drug had developed reviewing the nicotine patch, and due to its authority over research and marketing of controlled substances, Pilot Drug and its associated Drug Abuse Advisory Committee were logical places within FDA for Dr. Kessler to seek support for his efforts to obtain FDA authority to regulate tobacco. The struggle to regulate tobacco was the single most controversial effort that Dr. Kessler undertook while Commissioner of FDA. Within Pilot Drug, Dr. Wright became the point person on the tobacco issue. As Dr. Spyker noted, “Curtis was being groomed for control of nicotine.”⁵²¹ Dr. Spyker recalled Dr. Wright once saying the same thing.

On August 1, 1994, the Drug Abuse Advisory Committee held hearings about the addictive nature of cigarettes. The Committee listened to testimony comparing tobacco to heroin, cocaine and alcohol. Dr. Wright guided the committee throughout its deliberations.⁵²² On August 2, the Committee issued a report concluding that nicotine in the cigarette dosage form was an addictive drug. Dr. Kessler stated, "It changes the way we have to look at the whole issue...[smoking is not] just an issue of free choice," as the tobacco industry claimed.⁵²³

According to Dr. Kessler, there were two criteria that had to be established before tobacco could come under the purview of the FDA; it had to alter the structure and function of the body and the manufacturer had to produce it with the intent of ensuring that it had an effect on the body. Dr. Wright expressed the view that the next step was for FDA to "write a regulation." Needless to say, these actions of Dr. Kessler, the Drug Abuse Advisory Committee and Dr. Wright generated a ferocious and sustained attack from the tobacco industry and its allies in Congress.⁵²⁴ Pilot Drug's potential political vulnerability

⁵²⁰Dr. Curtis Wright interview, in Pellerin C. *Trips: How Hallucinogens Work in Your Brain* Seven Stories Press: New York, 1999: 164.

⁵²¹personal communication, Dr. Spyker, February 22, 1999.

⁵²²Schuster L. FDA Panel Says Cigarettes are Addictive. *UPI Wire Service*August 2, 1994.

⁵²³Ibid.

⁵²⁴FDA's lack of authority to regulate tobacco was decided in a U.S. Supreme Court case argued December 1, 1999 and decided March 21, 2000, *FDA v. Brown and Williamson Tobacco Corp.*,120 S. Ct. 1291 (2000). According to the majority opinion delivered by Justice O'Conner, “ In 1996, the FDA asserted jurisdiction to regulate tobacco products, concluding that, under the FDCA, nicotine is a “drug” and cigarettes and smokeless tobacco are “devices” that deliver nicotine to the body. Pursuant to this authority, the FDA promulgated regulations governing tobacco products’ promotion, labeling, and accessibility to children and adolescents...Respondents, a group of tobacco manufacturers, retailers, and advertisers, filed this

regarding its psychedelic and medical marijuana approvals pales in comparison to the risky nature of its role in the tobacco regulation controversy.⁵²⁵

IOM Report on Development of Medications For the Treatment of Addiction

FDA's effort to regulate rather than restrict research with psychedelic drugs and marijuana was given somewhat unexpected support by the publication in March 1994 of the preliminary report of an Institute of Medicine Study on the development of medications for the treatment of addiction.⁵²⁶ The IOM report identified a series of federal regulatory obstacles hindering the development of Schedule I drugs for the treatment of addiction. These obstacles were primarily created by the dual authority of the Drug Enforcement Administration (DEA) and the FDA over the conduct of clinical research with Schedule I drugs. The IOM report stated, "DEA requires that protocols for research with Schedule I controlled substances be submitted to it for approval... The practical consequences of this dual authority over clinical research, particularly in the light of the additional complication of multiple state laws patterned after the CSA [Controlled Substances Act of 1970], is a clinical research environment for scheduled drugs that is extraordinarily bureaucratic from the procedural point of view and unnecessarily difficult. That is especially true given the relatively small amounts of any controlled substance used in research; the consequences of diversion to public health would be small even if the diversion was substantial."⁵²⁷

The IOM report made the bold recommendation that DEA cede its authority to regulate research with all Schedule I substances to FDA.⁵²⁸ The IOM report primarily based its critique of excessive DEA regulations on the perceived need to expedite research and development of Schedule I drugs such as LAAM, methadone and other substitution-type medications used in the treatment of addiction. Nevertheless, IOM's recommendations applied to medical research with all Schedule I drugs, even psychedelics and marijuana, and for all medical applications including but not limited to the treatment of addiction. In the

suit challenging the FDA's regulations. They moved for summary judgment on the ground, *inter alia*, that the FDA lacked jurisdiction to regulate tobacco products as customarily marketed, that is, without manufacturer claims of therapeutic benefit. The District Court upheld the FDA's authority, but the Fourth Circuit reversed, holding that Congress has not granted the FDA jurisdiction to regulate tobacco products... Held: Reading the FDCA as a whole, as well as in conjunction with Congress' subsequent tobacco-specific legislation, it is plain that Congress has not given the FDA the authority to regulate tobacco products as customarily marketed. "

⁵²⁵It is difficult to say whether there were spillover effects between Pilot Drug's involvement in several different controversial regulatory issues.

⁵²⁶Fulco C. Liverman C, Earley L (eds.) *Development of Medications for the Treatment of Opiate and Cocaine Addictions: Issues for the Government and Private Sector*. Washington, DC Institute of Medicine, National Academy Press, 1995.

⁵²⁷*Ibid.*, 13.

⁵²⁸*Ibid.*, 13.

cases of the FDA-approved ibogaine and LSD protocols, which were explicitly focused on the treatment of drug dependence, the IOM arguments were directly on point. Though DEA did not formally cede its authority to the FDA, DEA oversight of Schedule I research protocols has not significantly impeded the conduct of psychedelic research. DEA oversight has been more problematic regarding medical marijuana research.

Medical Marijuana Research: FDA Says Yes

Early in 1994, Pilot Drug approved the first study in over a decade of the medical use of marijuana in a patient population.⁵²⁹ The protocol had been submitted by Dr. Donald Abrams, UC San Francisco, and was designed to investigate the use of marijuana in treating AIDS wasting syndrome, the same indication that had generated so many applications to FDA's Compassionate Use program.⁵³⁰ The protocol was designed as a randomized double-blind, placebo-controlled trial with three different treatment groups, low, medium or high potency (THC) marijuana.

The initial design had called for a completely inactive placebo dose. However, the Institutional Review Board at Dr. Abrams' AIDS research center had objected on ethical grounds to giving a placebo to people with a potentially fatal case of AIDS wasting when an unsatisfactory but marginally effective alternative medication, the oral THC pill, was commercially available.⁵³¹ As a result, the study was redesigned into a dose-escalation study with the low dose to be minimally active, with subjects receiving the low dose to be considered the placebo group. One advantage of using a low dose of the test drug as the placebo condition is that patients are not as likely to be able to determine from subjective clues whether they received a low, medium or high dose as they would be if trying to evaluate whether they had received a completely inactive placebo or a medium or high dose. One disadvantage of using a low dose group as the control is that the low dose may still offer some minimal efficacy, making it more difficult to show a statistically significant treatment difference between the high, medium and low dose groups.

In April 1994, Dr. Abrams submitted an application to DEA for a license to work

⁵²⁹IND # 43,542. A Prospective, Randomized Pilot Study of High, Medium or Low THC-content Smoked Marijuana on Weight Loss in Persons with HIV-related Wasting Syndrome versus Dronabinol (delta-9-tetrahydrocannabinol, Marinol, Roxane laboratories). <http://www.maps.org/mmj/v6proto.html> Dr. Abrams had begun the protocol development process in the summer of 1992, in association with this author who recruited Dr. Abrams for this project. MAPS donated \$10,000 to UC San Francisco as a contribution for the time that Dr. Abrams and associates spent on the protocol development process for the initial and subsequent protocol designs.

⁵³⁰Abrams D. Medical marijuana: tribulations and trials. *J Psychoact Drug* 30 (Apr-Jun 1998) 2:163-9.

⁵³¹The FDA had approved the oral-THC pill for AIDS wasting on the basis of clinical trials that had demonstrated increased appetite but not weight gain. Anecdotally, most AIDS-wasting patients strongly preferred smoked marijuana over the oral THC pill.

with marijuana in his FDA-approved study. The application was submitted to Mr. Gene Haislip, DEA Deputy Assistant Administrator, Office of Diversion Control, who licenses researchers to work with Schedule I drugs. On June 8, 1994, Mr. Haislip sent a letter to FDA Commissioner Dr. Kessler outlining DEA's objections to the protocol, not all of which had to do with ensuring that research supplies of marijuana were not diverted to non-medical uses.⁵³² DEA questioned the credentials of the principal investigator, the worthiness of the scientific design of the trial, and the credibility and legal status of the Dutch company that was working to provide marijuana for the study.⁵³³ Furthermore, Mr. Haislip challenged FDA authority by writing, "DEA normally relies on FDA's findings with regard to such issues as the purpose of the study, the source and purity of the material, and the methods used to insure scientific integrity. The DEA will not proceed with the registration process for Dr. Abrams until and unless the above issues are adequately determined by FDA. We believe that FDA has the same interest and commitment as the DEA, and shares the same desire to protect the public from bogus, politicized activities masquerading as medical science." Mr. Haislip also worried about the consequences of the study generating data suggesting the efficacy of marijuana for AIDS wasting, arguing "Given the history and zeal of marijuana advocates, it is likely that if marijuana shows any efficacy at all in this study, individuals will make claims that marijuana is at least as effective as dronabinol [the FDA-approved oral THC pill] and therefore has medical use."⁵³⁴

Dr. Kessler, uncomfortable with DEA interference in the design of scientific research protocols, forwarded the letter to Dr. Lee Brown, then-Director of the Office of National Drug Control Policy. On July 5, 1994, Dr. Brown wrote a firm letter to DEA Administrator Tom Constantine supporting FDA primacy in matters of research design and affirming the policy of permitting the exploration of the medical uses of Schedule I drugs. Mr. Brown wrote, "I have asked my deputy, Mr. Fred Garcia, to inform FDA (also enclosed) that at this time we do not wish a departure from established policy, which is to treat research on the therapeutic use of marijuana the same as research on any other drug of abuse potential. Nor do we wish to encourage a blurring of well-established responsibilities and working relationships. I am confident that I can count on your assistance in maintaining established policy in this area."⁵³⁵

⁵³²Haislip G. Deputy Assistant Administrator, DEA Office of Diversion Control. Letter to Dr. David Kessler, FDA Commissioner. June 8, 1994. This four-page letter was obtained through Freedom of Information Act request and subsequent litigation by the Public Citizen Litigation Group on behalf of the Marijuana Policy Project (MPP). FOIA Request 96-0397.

⁵³³Abrams D. (1998): 165.

⁵³⁴Haislip letter, June 8, 1994: 3-4.

⁵³⁵Brown L. Director, Office of National Drug Control Policy. Letter to DEA Administrator Tom Constantine. July 5, 1994. This letter was obtained by FOIA request by MPP, without need of additional litigation.

Mr. Fred Garcia clarified Dr. Brown's views in his July 5, 1994 letter to Dr. Kessler. Mr. Garcia remarked, "This Office is very cognizant of the fact that certain drugs with significant abuse potential can also have important, if limited, medical uses. We believe, and I'm sure you will agree, that effective drug control policy is consistent with policy that encourages credible medical research and fosters legitimate medical practice."⁵³⁶

On August 3, 1994, Dr. Janet Woodcock, FDA Director of the Center for Drug Evaluation and Research (CDER) wrote a substantive, firm and friendly letter to Mr. Haislip responding to many of the issues he raised in his initial letter to Dr. Kessler. She defended FDA's review of the protocol, then remarked, "We are pleased to see a physician oncologist of Dr. Abrams' caliber serving as principal investigator and we believe his involvement is strong evidence of well-meaning intentions concerning the patients' welfare and of the research team's commitment to development of an adequate and well-controlled study. While you are correct that we cannot prevent misuse of results from this study, the sponsor has provided a Clinical Plan⁵³⁷ and identified this study as a pilot study. The initial pilot study allows the sponsor to refine the methodologies and permit an estimate of sample size for a larger study. Such an approach is consistent with good drug development practices."⁵³⁸ She concluded by noting, "I believe the meetings held between FDA and DEA staffs demonstrate that it is mutually beneficial for the agencies to continue to coordinate on drug abuse-related matters. We appreciate your concerns and look forward to working with you on this important issue."

This exchange of letters illustrates the resilience of Pilot Drug's policies toward research with Schedule I drugs. Faced with strong DEA pressure, senior management at FDA with the backing of the Director of the Office of National Drug Control Policy endorse in almost exactly the same words used by Pilot Drug and the Drug Abuse Advisory Committee, namely that FDA will review the medical use of psychedelics and marijuana in the same manner and with the same procedures that FDA reviews other drugs of abuse, and indeed all other drugs.

In August 1994, Dr. Abrams went ahead and submitted an application to NIDA for 5.7 kilograms of marijuana for his dose-escalation study. He decided not to pursue his application for a DEA license until after he had an approved protocol and source of

⁵³⁶Garcia F. Deputy Director, Office of National Drug Control Policy, Office for Demand Reduction. Letter to Dr. David Kessler, FDA Commissioner. July 5, 1994. This one-page letter was obtained by FOIA request by MPP, without need of additional litigation.

⁵³⁷Doblin R. A Comprehensive Clinical Plan for the Investigation of Marijuana's Medical Use in the Treatment of the HIV-Related Wasting Syndrome. *Bull MAPS*5 (Summer 1994) 1:16-17.
<http://www.maps.org/news-letters/v05n1/05116cli.html>

⁵³⁸Woodcock J. FDA Director of Center for Drug Evaluation and Research. Letter to Mr. Gene Haislip, DEA Deputy Assistant Administrator, Office of Diversion Control. August 3, 1994. This two-page letter was obtained by FOIA request by MPP, without need of additional litigation.

marijuana for the study.

Psychedelic Research In Switzerland

In early 1995, a team of Swiss scientists at the University of Zurich published their first psychedelic research paper, reporting on the development of a method to measure ketamine in blood plasma.⁵³⁹ This paper marked the cautious resumption of psychedelic research after the Swiss Ministry of Health had withdrawn permission in 1993 from several psychiatrists who had been administering LSD and MDMA to their patients, though without generating scientific data about their work. The Swiss team, soon to be directed by Dr. Franz Vollenweider, began conducting a series of basic pharmacological and psychological studies utilizing the most advanced scientific methods including PET scans into the effects, though not psychotherapeutic uses, of a variety of psychedelics including psilocybin,^{540 541 542 543} ketamine,^{544 545 546} and MDMA.^{547 548 549 550}

⁵³⁹ Feng N, Vollenweider F, Minder E, Rentsch K, Grampp T, Vonderschmitt D. Development of a gas chromatography-mass spectrometry method for determination of ketamine in plasma and its application to human samples. *Ther Drug Monit* 17 (Feb. 1995) 1:95-100.

⁵⁴⁰Vollenweider F, Leenders K, Scharfetter C, Maguire P, Stadelmann O, Angst J. Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. *Neuropsychopharm*16 (May 1997) 5:357-72.

⁵⁴¹Hasler F, Bourquin D, Brenneisen R, Bar T, Vollenweider F. Determination of psilocin and 4-hydroxyindole-3-acetic acid in plasma by HPLC-ECD and pharmacokinetic profiles of oral and intravenous psilocybin in man. *Pharm Acta Helv* 72 (Jun 1997) 3:175-84.

⁵⁴²Vollenweider F, Vollenweider-Scherpenhuyzen M, Babler A, Vogel H, Hell D. Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. *Neuroreport* 9 (Dec. 1, 1998) 17:3897-902.

⁵⁴³Vollenweider F, Vontobel P, Hell D, Leenders K. 5-HT modulation of dopamine release in basal ganglia in psilocybin-induced psychosis in man--a PET study with [11C]raclopride. *Neuropsychopharm*20 (May 1999) 5:424-33.

⁵⁴⁴Vollenweider F, Leenders K, Scharfetter C, Antonini A, Maguire P, Missimer J, Angst J. Metabolic hyperfrontality and psychopathology in the ketamine model of psychosis using positron emission tomography (PET) and [18F]fluorodeoxyglucose (FDG). *Eur Neuropsychopharmacol* 7 (Feb 1997) 1:9-24.

⁵⁴⁵Vollenweider F, Leenders K, Oye I, Hell D, Angst J. Differential psychopathology and patterns of cerebral glucose utilisation produced by (S)- and (R)-ketamine in healthy volunteers using positron emission tomography (PET). *Eur Neuropsychopharmacol* 7 (Feb 1997) 1:25-38.

⁵⁴⁶Vollenweider F, Vontobel P, Oye I, Hell D, Leenders K. Effects of (S)-ketamine on striatal dopamine: a [11C]raclopride PET study of a model psychosis in humans. *J Psychiatr Res* 34 (Jan-Feb 2000) 1:35-43.

⁵⁴⁷Vollenweider F, Gamma A, Liechti M, Huber T. Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naïve healthy volunteers. *Neuropsychopharm*19 (Oct 1998) 4:241-51.

Ibogaine Research: FDA YES, NIDA-NO.

On March 8, 1995, NIDA/MDD, with FDA participation, convened an Ibogaine protocol development meeting. The purpose of the meeting was to review the existing research and evaluate whether to proceed to conduct the first trial in human subjects. Up to this point, MDD had spent over \$1 million dollars on preclinical research.⁵⁵¹ The outcome of the meeting was a decision by MDD not to proceed into clinical trials. MDD expressed concerns about neurotoxicity, the possibility of a fatal adverse event, and the difficulties, uncertainties and expense of taking ibogaine through the drug development process.

On March 10, 1995, Dr. Wright sent a memo to Dr. Frank Vocci, Director of NIDA's Medication Development Division, urging NIDA to help facilitate ibogaine research by offering a grant for a small Phase I safety study. Dr. Wright commented,

I believe that it is in the public's best interests that research with ibogaine go forward...The methods of the major pharmaceutical firms are without equal in developing a new drug in a manner that produces a safe and effective pharmaceutical. The FDA staff have grown to respect the ability of commercial scientists in this regard. They are really outstanding at what they do. Unfortunately, they do not usually produce breakthrough products or new indications. These are most frequently initiated either by venture capital firms, subsidiaries of major firms formed to take risks, iconoclasts within industry, or individual physicians. In my opinion, the normal process of peer review is excellent at deciding how best to undertake research in a new area, but often not a good way to decide if to undertake original new research. My recommendation is to use your strength to help those who will undertake such risks. ⁵⁵²

⁵⁴⁸Vollenweider F, Remensberger S, Hell D, Geyer M. Opposite effects of 3,4-methylenedioxymethamphetamine (MDMA) on sensorimotor gating in rats versus healthy humans. *Psychopharm (Berl)* 143 (Apr 1999) 4:365-72.

⁵⁴⁹Vollenweider F, Gamma A, Liechti M, Huber T. Is a single dose of MDMA harmless?. *Neuropsychopharm* 21 (Oct 1999) 4:598-600.

⁵⁵⁰Gamma A, Frei E, Lehmann D, Pascual-Marqui R, Hell D, Vollenweider F. Mood state and brain electric activity in ecstasy users. *Neuroreport* 11 (Jan 17, 2000) 1:157-62.

⁵⁵¹On November 5, 1999, Dr. Frank Vocci, Director of NIDA/MDD, spoke at an ibogaine conference held at New York University School of Medicine. In response to a question, Dr. Vocci said that NIDA had spent about \$2 million to date on ibogaine preclinical research.

⁵⁵²Wright C. Acting Director, FDA Pilot Drug Evaluation Staff. Memorandum to Dr. Frank Vocci, NIDA Director of Medications Development Division, March 10, 1995. Alper K. (ed.) *First International Conference on Ibogaine: Syllabus, Nov. 5 & 6, 1999*. New York University School of Medicine: 428-431. This document was obtained through a FOIA request of FDA by Howard Lotsof.

Dr. Wright's letter was not sufficiently persuasive. NIDA/MDD decided not to make any grants available for a pilot clinical trial into the potential use of ibogaine in easing withdrawal from opiates.

On May 27, 1995, Pilot Drug reviewed ibogaine data from the lowest dose group tested by Dr. Sanchez-Ramos and Dr. Mash, then gave Dr. Mash and Dr. Sanchez-Ramos permission to move to the 2 mg/kg dose level.⁵⁵³ Dr. Mash and Dr. Sanchez-Ramos were able to obtain funding to treat all subjects at the 2 mg/kg dose.⁵⁵⁴ Dr. Mash and Dr. Sanchez-Ramos then used the results as pilot data in an NIH grant application, which was rejected.⁵⁵⁵ The only FDA-approved ibogaine project subsequently collapsed for lack of funds.^{556 557 558} The cost of the Phase I trial was in excess of \$500,000, more than could be raised by the advocates of ibogaine research. Foundation money for this sort of research seemed unobtainable

Medical Marijuana Research- NIDA Just Says NO

On April 19, 1995, after sitting on Dr. Abrams' request for almost nine months, Dr. Alan Leshner, Director of NIDA, sent a letter to Dr. Abrams rejecting his request for marijuana.⁵⁵⁹ A substantial portion of Dr. Leshner's rationale was based on the argument that the study should not have been designed as a pilot study because the results could be easily misinterpreted, quite similar to Mr. Haislip's perspective.⁵⁶⁰ Dr. Abrams responded with a rather angry letter to Dr. Leshner, and determined to keep trying.⁵⁶¹ Dr. Leshner's rejection led to a silent protest by medical marijuana advocates at NIDA's July 1995

⁵⁵³personal communication, Dr. Deborah Mash, August 31, 1999.

⁵⁵⁴\$25,000 of the costs of the 2 mg/kg dose level were funded by MAPS while another \$25,000 was sent by a donor directly to the University of Miami, at the request of MAPS.

⁵⁵⁵personal communication, Dr. Mash, August 31, 1999.

⁵⁵⁶personal communication, Dr. Mash, August 31, 1999.

⁵⁵⁷Mash D, Kovera C, Buck B, Norenberg M, Shapshak P, Hearn L and Sanchez-Ramos J. Medication Development of Ibogaine as a Pharmacotherapy for the Treatment of Drug Dependence. Ali S. (ed.) Neurochemistry of Drugs of Abuse- Cocaine, Ibogaine and Substituted Amphetamine. *Ann N Y Acad Scien* 844 (1998): 274-292.

⁵⁵⁸Staff. Data Accrue on "Visionary" agent to interrupt addiction. *Lancet* 354 (November 27, 1999): 1883.

⁵⁵⁹Leshner A. Director of NIDA. Letter to Dr. Donald Abrams. April 19, 1995.

<http://www.maps.org/mmj/leshner.html>

⁵⁶⁰For a critique of Dr. Leshner's arguments by this author, see Doblin R. NIDA Blocks Medical Marijuana Research. <http://www.maps.org/mmj/ricklesh.html>

⁵⁶¹Abrams D. Letter to Dr. Leshner, Director of NIDA. April 28, 1995.

<http://www.maps.org/mmj/abrams.html>

scientific conference on marijuana, attended by Dr. Leshner, HHS Secretary Donna Shalala and Director of the Office of National Drug Control Policy Mr. Lee Brown. As a result of the protest, Dr. Leshner invited several proponents of medical marijuana research to a private meeting.⁵⁶² During that meeting, Dr. Leshner indicated that NIDA would be willing to supply Dr. Abrams with the necessary marijuana for an FDA-approved study, but only after a formal NIH grant application had been evaluated and approved for funding by the NIH grant-review system.⁵⁶³ Dr. Leshner explained that NIDA needed to ensure that the protocol was “scientifically meritorious,” and that in his opinion mere FDA approval of the protocol was inadequate for this purpose. According to Dr. Leshner, FDA reviews protocols primarily from the perspective of an IRB looking out for the safety of the human subjects and not from the perspective of a critical scientist seeking to ensure good quality research. In his view, only the NIH peer review system was sufficiently rigorous to review protocols for scientific merit, therefore only protocols that were submitted to NIH and awarded funding would receive marijuana from NIDA.

From Pilot Drug to Anesthetics, Critical Care and Addiction Drug Products

The FDA itself heralded its new openness to psychedelic research in an article entitled “Medical Possibilities for Psychedelic Drugs” which appeared in the September 1995 issue of FDA’s magazine, the *FDA Consumer*.⁵⁶⁴ The article favorably reviewed the projects that had been approved by Pilot Drug and spoke in positive terms about the potential therapeutic benefits that might be developed as a result of the renewed opportunities for research. The possibility of using psychedelics as probes to conduct basic research into the properties of the mind was also mentioned as an exciting possibility for future studies, picking up where the field left off when research was truncated for largely political reasons.

In October 1995, just one month later, Pilot Drug was dissolved and the portfolio of drugs it reviewed were redistributed to other Divisions. [Chapter 3 analyzes why Pilot Drug was dissolved, and contains organizational charts.] Dr. Janet Woodcock, FDA’s new Director of the Center for Drug Evaluation and Research (CDER), reorganized CDER in response to the new funding for staff made available to FDA as a result of the Prescription Drug User Fee Act of 1992 (PDUFA).

Dr. Woodcock enlarged the number of Divisions and Offices in an effort to reduce the pyramidal nature of the FDA hierarchy, thus enabling more people to review and sign off on NDAs. The responsibility for the review of research protocols for Schedule I drugs was transferred to the newly created Division of Anesthetics, Critical Care and Addiction

⁵⁶²The protest was organized by this author.

⁵⁶³Abrams (1998): 166.

⁵⁶⁴Kurtzweil P. Medical Possibilities for Psychedelic Drugs.” *FDA Consum* September 1995.

http://www.fda.gov/fdac/features/795_psych.html

Drug Products (DACCADP).⁵⁶⁵ Dr. Curtis Wright, Acting-Director of Pilot Drug when it was dissolved, was appointed Acting-Director of DACCADP, pending the completion of a formal hiring process for the permanent directorship.

Medical Marijuana Research Finally Approved by FDA and NIDA

In May 1996, Dr. Abrams submitted a protocol to NIH for review, following up on Dr. Leshner's promise to supply marijuana if the NIH grant-review process approved and funded Dr. Abrams protocol.⁵⁶⁶ In August 1996, NIH rejected Dr. Abrams' revised protocol. One reviewer stated, "The biggest difficulty with the design is the small sample size, in light of weak support for effect sizes or power," seemingly overlooking Dr. Abrams' intention to conduct a pilot study.⁵⁶⁷ Another commented, "Why the investigator choose marijuana smoking as a potential intervention drug for HIV-related anorexia and weight loss is not at all clear, given the knowledge that marijuana smoking may result in immune suppression and respiratory disease, and that marijuana itself may be carcinogenic. What is the long-term effect of marijuana smoking on the patients with HIV infection and AIDS?"⁵⁶⁸ This second reviewer seemed to want answers that could only come from research before the research could begin.

External pressures on NIDA to permit medical marijuana research started to build with the November 1996 elections, when voters in Arizona and California passed initiatives that removed state prohibitions against the medical use of marijuana for patients who had the support of their physicians.⁵⁶⁹

On December 2, 1996, Senate Judiciary Committee Hearings chaired by Sen. Orrin Hatch were held, primarily to express Senatorial disapproval of the use of ballot initiatives to advance the medical use of marijuana.⁵⁷⁰ Instead, Senators argued that the medical use of

⁵⁶⁵personal communication, Dr. Wright, March 8, 1999.

⁵⁶⁶Abrams D. Research Plan Portion of Public Health Service Grant Application. Protocol: Smoked Marijuana for HIV-Associated Anorexia and Wasting. Submitted to the National Institutes of Health, April 1996. <http://www.maps.org/mmj/abrams2.shtml>

⁵⁶⁷Deyton L. National Institute of Allergy and Infectious Diseases. Letter to Dr. Donald Abrams. Notification of Scientific Review Action, Application # 1R01AI40866-01, Smoked Marijuana for HIV-Associated Anorexia and Wasting Protocol. August 22, 1996. <http://www.maps.org/mmj/abrams1.shtml>

⁵⁶⁸Ibid., Comments of Reviewer #3.

⁵⁶⁹In California, the initiative stated that physicians were authorized to "recommend" the medical use of marijuana, while in Arizona the initiative stated that physicians were authorized to "prescribe" the medical use of marijuana.

⁵⁷⁰Arizona and California Medical Drug Use Initiatives. Hearing of the Senate Judiciary Committee, chaired by Sen. Orrin Hatch (R-UT). December 2, 1996.

marijuana should be settled with scientific research conducted under the auspices of the FDA. Sen. Hatch remarked, "it is a mistake in my opinion to abandon our principles, the law and modern science in the name of compassion."⁵⁷¹ In his prepared statement, Sen. Hatch stated, "The only way to determine the medical utility of any drug is to rely on our well-established FDA review process."⁵⁷² Sen. Hatch also questioned the Arizona initiatives approval of the right of physicians to prescribe all Schedule I drugs if research suggested they could be helpful.⁵⁷³ Sen. Hatch then held up a newsletter from a non-profit organization that supports psychedelic and medical marijuana research.⁵⁷⁴ He read from a list of proposed psychedelic research projects, in order to show that Arizona physicians could cite those studies to justify prescribing psychedelics. Sen. Hatch's planned expression of outrage turned defensive when the first two projects he read from the list were for the use of psychedelics for the treatment of substance abuse. Sen. Hatch then felt compelled to state that he wasn't saying that research shouldn't take place.⁵⁷⁵

On December 30, 1996, Gen. Barry McCaffrey, Director of the White House Office of National Drug Policy (ONDCP), Attorney General Janet Reno and Donna E. Shalala, the Secretary of Health and Human Services, gathered at a joint press conference to threaten physicians who prescribed marijuana to their patients with the loss of their prescription-writing privileges and the possibility of criminal charges.⁵⁷⁶ ⁵⁷⁷ By January

⁵⁷¹Transcript of the Senate Judiciary Committee hearing prepared by Federal News Service.

⁵⁷²Prepared Statement of Senator Orrin G. Hatch, Chairman. Arizona and California Medical Drug Use Initiatives. Senate Judiciary Committee hearing. December 2, 1996.

⁵⁷³Proposition 200 states, "Notwithstanding any law to the contrary, a medical doctor must document that scientific research exists which supports the use of a controlled substance listed in Schedule I of Section 36-25.12 to treat a disease or to relieve the pain and suffering of a seriously ill or terminally ill patient before prescribing the controlled substance." Physicians were also required to obtain written support from another physician for any such use.

⁵⁷⁴The organization that published the newsletter was the Multidisciplinary Association for Psychedelic Studies (MAPS).

⁵⁷⁵This exchange is missing from the transcript of the hearing prepared by Federal News Service. A videotape of the hearing sold by C-Span contains this portion of the exchange.

⁵⁷⁶McCaffry B. Director of the Office of National Drug Control Policy. The Administration's Response to the Passage of California Proposition 215 and Arizona Proposition. December 30, 1996.

<http://www.ncjrs.org/txtfiles/215rel.txt>

⁵⁷⁷Staff. Doctors Given Federal Threat On Marijuana. *New York Times*.December 31, 1996: A1. "The Clinton Administration said today that doctors in California and Arizona who prescribe drugs like marijuana that are illegal under Federal law could lose their prescription-writing privileges and even face criminal charges." see also, Wren C. Doctors Criticize Move Against State Measures. *New York Times*.December 31, 1996.

7, 1997, the negative reaction to the Administration's threats against physicians by the California Medical Association,⁵⁷⁸ the San Francisco Medical Society⁵⁷⁹ and by many media commentators,⁵⁸⁰ along with the external pressure generated by the November 1996 passage of the California and Arizona initiatives, proved sufficiently powerful to motivate Gen. McCaffrey to allocate \$1 million to the Institute of Medicine to fund an 18-month review of the scientific data about marijuana's medical uses. The purpose of the review was to "provide a comprehensive assessment of the state of scientific knowledge and to identify gaps in the knowledge base about marijuana."⁵⁸¹

In January 1997, Dr. Abrams met in person with Dr. Leshner at NIDA headquarters in Rockville, Maryland. The meeting was cordial. Dr. Leshner encouraged Dr. Abrams to submit yet another grant application for the May 1, 1997 grant cycle.⁵⁸²

On February 19-20, 1997, the National Institutes of Health convened a conference on the Medical Utility of Marijuana.⁵⁸³ The purpose of the NIH conference was virtually identical to that of the IOM report commissioned by Gen. McCaffrey. Speakers at the conference, called the Ad Hoc Group of Experts, were all chosen by NIH. These experts reviewed and summarized the existing research literature and also accepted public comment.⁵⁸⁴ In addition, FDA's Dr. Robert Temple offered very helpful suggestions for the design of clinical trials investigating the medical use of marijuana. The chair of the conference was Dr. William Beaver, Professor of Pharmacology and Anesthesia, Georgetown University School of Medicine. In the report on the conference sent to Dr. Harold Varmus, the Director of NIH, Dr. Beaver states, "For at least some potential indications, marijuana looks promising enough to recommend that there be new controlled studies done."⁵⁸⁵ The Ad Hoc Group of Experts also recommended that, "Whether or not

⁵⁷⁸Mead A. Proposition 215: A Dilemma. *J Psychoact Drug*30(Apr-June1998) 2:149-154.

⁵⁷⁹Wells D. Casenote: Conant V. McCaffrey: Physicians, Marijuana, and the First Amendment. *70 U Colo L Rev*975 (Summer 1999).

⁵⁸⁰Scheer R. Reefer Madness, '90's Style: The war on drugs has been a dismal failure and its escalation to fight marijuana is lunacy. *Los Angeles Times*, December 31, 1996: A7.

⁵⁸¹Staff. Government to Spend \$1 Million Studying Marijuana as Medicine. *NY TImes*January 9, 1997:B:10.

⁵⁸²Abrams (1998): 167.

⁵⁸³Workshop on the Medical Utility of Marijuana: Report to the Director, National Institutes of Health. National Institutes of Health, February 19-21, 1997.

<http://www.nih.gov/news/medmarijuana/MedicalMarijuana.htm>

⁵⁸⁴Doblin R. Turning Protests into Protocols: Dr. Harter's Legacy. Submitted to the NIH Expert Committee on the Medical Utility of Marijuana. February 25, 1997.

<http://www.maps.org/mmj/022597mmj.shtml>

⁵⁸⁵Executive Summary, Question Three. Workshop on the Medical Utility of Marijuana: Report to the Director, National Institutes of Health. National Institutes of Health, February 19-21, 1997.

the NIH is the primary source of grant support for a proposed bona fide clinical research study, if that study meets U.S. regulatory standards (U.S. Food and Drug Administration (FDA) protocol approval and Drug Enforcement Administration (DEA) controlled substances registration) the study should receive marijuana and/or matching placebos supplied by the National Institute on Drug Abuse (NIDA). In this way, a new body of studies may emerge to test the various hypotheses concerning marijuana.”⁵⁸⁶ Dr. Varmos never issued a formal response to the recommendations of NIH’s Ad Hoc Group of Experts.

In August 1997, NIH approved Dr. Abrams’ revised protocol and awarded him a grant of \$978,000 and a supply of NIDA marijuana.⁵⁸⁷ The first patient was enrolled into the study in May 1998, almost six years after Dr. Abrams began the process of seeking approval to study the use of marijuana in AIDS patients. The protocol that Dr. Abrams was finally permitted and funded to conduct had been modified from the initial design of an efficacy study in AIDS wasting patients into a safety study in HIV+ individuals who do not have wasting. The new study was designed primarily to evaluate the pharmacokinetic interactions between marijuana and protease inhibitors, but will still be able to gather some data about dietary intake and weight. Regardless of the changes in design, this study represents a major breakthrough in medical marijuana research.⁵⁸⁸

NIDA’s June 17, 1997 Guidelines for Drug Abuse Research

On June 17, 1997, NIDA’s National Advisory Council on Drug Abuse issued its own set of recommended guidelines for drug abuse research that involved the administration of drugs to human subjects.⁵⁸⁹ ⁵⁹⁰ These guidelines, which were issued as advisory only and were not formal regulations, dealt with issues arising from the administration of controlled substances to research subjects. The NIDA guidelines were issued for use by local IRBs, the Initial Review Groups (IRGs) of outside experts that

⁵⁸⁶Ibid.

⁵⁸⁷For an overview of the protocol that was finally accepted, see <http://www.maps.org/mmj/proto.htm>.

⁵⁸⁸Dr. Abrams enrolled the last patient in his study in May 2000. As of June 12, 2000 there are no researchers in the United States studying any medical use of marijuana in any patient population. Dr. Abrams will complete his data analysis in late June 2000.

⁵⁸⁹Recommended Guidelines for the Administration of Drugs to Human Subjects. National Advisory Council on Drug Abuse. June 17, 1997. <http://www.nida.nih.gov:80/HSGuide.html>

⁵⁹⁰In July 1997, Dr. Michael Klein, one of the few DACCADP staff who was also an early volunteer at Pilot Drug, presented a paper explaining DACCADP’s policies toward the development of medications to treat cocaine addiction, discussing outcome measures and protocol design issues. Klein M. Research Issues Related to Development of Medications for Treatment of Cocaine Addiction. *Neurochemistry of Drugs of Abuse- Cocaine, Ibogaine and Substituted Amphetamine*, ed. by Ali S. New York: Annals of the New York Academy of Sciences. 844 (1998): 75-91.

evaluated and ranked all grant applications submitted to NIDA as well as all other Institutes of the National Institutes of Science, and the National Advisory Councils (NACs) of NIDA and the other Institutes that have final review over all grants given by the Institutes. Among the matters covered by the guidelines were issues related to subject selection, the inclusion of subjects who were already addicted to drugs, forms of payment for participating in research, the prior or current drug treatment status of subjects, and confidentiality of records.

The NIDA-funded MDMA studies of Dr. Jones and Drs. Tancer and Schuster had both been approved by DACCADP during the time these guidelines were being developed. Dr. Jones was a co-author of the guidelines. According to the guidelines, “It is expected that research involving the administration of drugs to individuals who have never used drugs prior to study participation would occur only in the rarest of circumstances and with the strongest justification.”⁵⁹¹ These guidelines lent support for FDA’s requirement that subjects in these two studies be restricted to those with prior exposure to MDMA. Part of the rationale for this requirement was that the subjects would have already acquired a direct understanding of the risks of MDMA, primarily the possibility of neurotoxicity and the potential development of dependency or addiction to MDMA. This prior experience enhanced the ability of the subjects to give informed consent. In addition, by using subjects who had already chosen to self-administer MDMA, the researchers did not run the risk of initiating a pattern of drug use behavior in drug-naïve subjects. Furthermore, since subjects would already have had experience with MDMA, negative reactions to the experience of taking the drug in the context of a potentially disconcerting clinical research setting would be minimized.

One limitation of the use of subjects with prior exposure to MDMA is that prior use could act as a confound in studies that sought to evaluate the neurotoxic or neuropsychological consequences of a single dose of MDMA. In these instances, the two approved MDMA studies were not looking to evaluate effects in MDMA-naïve subjects but were designed to gather pharmacokinetic data and to explore drug discrimination effects, neither of which would be significantly compromised by using subjects who were experienced with MDMA. Nevertheless, the use of only MDMA-experienced subjects introduces a selection bias that ensures that the data will not be completely generalizable to MDMA-naïve subjects. The selection bias could serve to exclude people who might metabolize or perceive the subjective effects of MDMA differently than the norm.

Two NIDA-Funded MDMA Research Projects Approved by FDA

During the summer of 1997, Dr. Wright and the DACCADP reviewed and approved two NIDA-funded projects that involved the administration of MDMA to human subjects. Both these studies were basic Phase I research projects and were not

⁵⁹¹Recommended Guidelines for the Administration of Drugs to Human Subjects. Section: Administration of Drugs to Individuals Who Have Never Used Drugs.

therapeutically-oriented. One of the MDMA projects was a pharmacokinetic study to be conducted under the direction of Dr., Reese Jones, UC San Francisco.⁵⁹² The second NIDA-funded MDMA project is being conducted at Wayne State University School of Medicine by Dr. Manny Tancer and Charles Schuster, Ph.D., the ex-director of NIDA. The study involves the administration of MDMA and several other drugs to probe the interaction of the serotonin and dopamine systems.⁵⁹³ In both these studies, subjects were restricted to those who already had self-administered MDMA.

ERA OF RETREAT (1997- MID 1999)

Dr. Curtis Wright's Departure

During the time that Dr. Wright was competing for the position of permanent Director of DACCADP, most of the people who had created and supported Pilot Drug and believed in the value of that experiment were no longer at FDA. Dr. Peck left FDA in November 1, 1993.⁵⁹⁴ Dr. Harter left Pilot Drug shortly thereafter. Pilot Drug itself was dissolved in October 1995. (These restructurings and personnel changes will be discussed in Chapter 3.)

Dr. Kessler, who had worked with Dr. Wright on tobacco issues, had resigned as of February 28, 1997.⁵⁹⁵ Without top leadership in place at FDA, there was a chance that some FDA staff might become more reluctant to make what they thought might be controversial decisions, since they couldn't know how those decisions would be evaluated by whomever would become the next Commissioner.

Late in the summer of 1997, Dr. Woodcock decided to appoint Dr. Cynthia McCormick as permanent Director of DACCADP, passing over Dr. Wright for that position. Dr. McCormick had previously served as Deputy Director of the Neuropharmacologic Drug Division under Dr. Leber, whose antagonism to psychedelic research was well known.

⁵⁹²IND 53,648. Approved July 10, 1997. Preliminary data reported in: Everhart E, Jacob III P, Shwonek P, Baggott M, Jones R, Mendelson J. Estimation of the Metabolic Disposition of MDMA and MDA Enantiomers in Humans. *Abstracts—College on Problems of Drug Dependence (CPDD) 1999 Annual Meeting*, June 12-17, 1999: 41.

⁵⁹³IND 53,394. Approved July, 1998. The study is described in: Tancer M, Schuster C. Serotonin and Dopamine System Interactions in the Reinforcing Properties of Psychostimulants: A Research Strategy. *Bull MAPS* 7 (1997) 3:5-11. <http://www.maps.org/news-letters/v07n3/07305tan.html> This article is based on a grant application to NIDA which was subsequently approved for funding.

⁵⁹⁴McLearn D. *FDA Press Release P93-19*. March 18, 1993.

⁵⁹⁵Dr. Michael A. Friedman, MD, Former Deputy Commissioner for Operations, served as Acting Commissioner during the period between Dr. Kessler's resignation and Dr. Henney's appointment. Dr. Friedman became Lead Deputy and the Deputy Commissioner after Dr. Henney's appointment. He has since left the FDA.

In October 1997, shortly after Dr. Wright was passed over for the permanent position at DACCADP, he left the FDA for a job in the pharmaceutical industry.⁵⁹⁶ He had spent eight years at FDA, all with Pilot Drug and the DACCADP.

Marijuana Research- FDA Says No

Late in the Summer of 1997, shortly before Dr. Wright's departure, DACCADP refused to accept for review a medical marijuana protocol submitted by Dr. Ethan Russo, U. of Montana, and asked him formally to withdraw his application.⁵⁹⁷ Dr. Russo's protocol was designed to study the medical use of marijuana in treating people with migraine headaches that were not successfully treated by conventional medications. Unlike the approach taken with Dr. Abrams, DACCADP imposed a new requirement stating that before FDA would conduct its review, researchers seeking to investigate any medical use of marijuana first needed to obtain a supply of marijuana from the National Institute on Drug Abuse (NIDA).⁵⁹⁸ While this new policy served NIDA's interests, since it could say that it was not rejecting any FDA-approved protocols, it denied researchers the opportunity to consider the valuable comments and critiques about protocol design issues that are provided by FDA staff during the IND review process. Furthermore, FDA's policy was in direct contradiction to the recommendations of the 1997 NIH Workshop on the Medical Utility of Marijuana, which prioritized the FDA review process when it proposed that NIDA be required to automatically provide marijuana to all FDA-approved protocols.

Rather than protest, Dr. Russo accepted FDA's refusal to review his protocol and formally withdrew his application. He then went ahead and submitted his protocol to NIH in the Summer, 1997, without input from FDA.⁵⁹⁹ In Spring 1988, Dr. Russo received word that his grant application was rejected. In contrast to most of the reviewers of Dr. Abrams' grant applications, one reviewer thought the study design was too ambitious. Another thought patients should have to stay overnight at the hospital rather than being released after two hours. Another thought that all subjects who had ever smoked marijuana before should be excluded from the study.⁶⁰⁰ In the summer of 1998, DACCADP refused

⁵⁹⁶Staff. Adolor Corporation Appoints Two Executives; Dr. Curtis Wright to Lead Clinical and Regulatory Affairs; Peter J. Schied Named CFO. *PR Newswire* September 29, 1997.

⁵⁹⁷Russo E, Mielke J, Painter L, Hall S and Steele B. Cannabis in Acute Migraine Treatment Project. *Bull MAPS* 7 (1997) 3:16-17. <http://www.maps.org/news-letters/v07n3/07316rus.html>. MAPS has donated a total of \$8,000 to Dr. Russo from 1996-2000 for his efforts designing and seeking approval for his protocol.

⁵⁹⁸personal communication, Dr. Ethan Russo, August 18, 1999.

⁵⁹⁹<http://www.maps.org/news-letters/v07n3/07316rus.html>

⁶⁰⁰Russo E. Cannabis in acute migraine treatment project: Response to National Institutes of Health Critique. *Bull MAPS* 8 (1998) 1:15-17. <http://www.maps.org/news-letters/v08n1/08115rus.html>

once again to accept a revised protocol from Dr. Russo, reiterating its new policy that NIDA must agree to provide marijuana to the study before FDA would conduct its review of the protocol. This time, Dr. Russo refused to withdraw his IND application and insisted that it be officially rejected. He then went ahead and submitted a second NIH grant application, for the July 1, 1998 grant cycle.⁶⁰¹ On November 12, 1998, Dr. Russo learned that NIH had rejected his second grant application.⁶⁰² This time, the reviewers focused much of their criticisms on the supposed need for pilot data to supplement historical and anecdotal accounts, as if it were possible for Dr. Russo to gather pilot data somewhere else before submitting the NIH grant.

Orphan Drug Designation: FDA Says NO

Coincident with Dr. Russo's struggles with FDA, MAPS began to experience significant obstructions to research into the medical use of marijuana in a different FDA Division, the Office of Orphan Drug Development.⁶⁰³ On April 24, 1997, MAPS submitted an application to have marijuana designated an Orphan Drug for AIDS-wasting.⁶⁰⁴

In 1983, Congress had created the Orphan Drug program to provide incentives for the development of drugs for rare diseases for which the pharmaceutical industry saw no profit potential.⁶⁰⁵ Pharmaceutical companies could expect limited revenue from drugs for such relatively small populations and usually decided not to invest scarce research money into the risky development of drugs with limited profit potential. To help stimulate development of drugs for these small patient populations, the Orphan Drug program provides a package of benefits that include tax incentives to investors,⁶⁰⁶ special grant

⁶⁰¹Russo E. Cannabis in Acute Migraine Treatment Project- NIH Application 1998.

<http://www.maps.org/mmj/98russoproto.html>

⁶⁰²Kitt C. National Institute of Neurological Disorders and Stroke. Letter to Dr. Ethan Russo. Notification of Scientific Review Action, Application # 1R01NS37550-01A1, Cannabis in Acute Migraine Treatment Project. January 7, 1999. <http://www.maps.org/mmj/russo2b.html>

⁶⁰³For an excellent overview of the history and operation of FDA's Orphan Drug program, see Basara L, Montagne M. *Searching for Magic Bullets: Orphan Drugs, Consumer Activism, and Pharmaceutical Drug Development*. New York: Pharmaceutical Products Press- An Imprint of Haworth Press. 1994. see also, Rohde D. The Orphan Drug Act: An Engine of Innovation? At What Cost? *Food Drug Law J* 55 (2000) 1:125-143.

⁶⁰⁴Doblin R. Request for Orphan Drug Designation for Smoked Marijuana in the Treatment of HIV-Associated Wasting Syndrome. April 24, 1997. <http://www.maps.org/mmj/odda/042497.html>

⁶⁰⁵Orphan Drug Act of 1983, 97 P.L. 414; 96 Stat 2049. January 4, 1983.

⁶⁰⁶Sec.4 of the Orphan Drug Act amended the IRS code to create 44 H. Clinical Testing Expenses for Certain Drugs for Rares Diseases of Conditions. 26 U.S.C. 44H.

programs,⁶⁰⁷ protocol assistance,⁶⁰⁸ and 7 years of patent protection to drugs that might not otherwise be patentable.⁶⁰⁹ In order to qualify for these incentives, the person or corporate entity that seeks to develop a particular drug needs to submit an application to the FDA's Office of Orphan Drug Development requesting that the Office designate a particular drug as an orphan drug for a specific illness. The application must contain information proving as convincingly as possible that the development expenses cannot be recovered from sales⁶¹⁰ or, as determined by the Secretary of HHS, that the target patient population is under 200,000 patients per year.⁶¹¹ The sponsor must also provide some reasonable rationale for thinking that the drug in question might possibly prove helpful to patients with the orphan disease.

At the time of MAPS application to have marijuana declared an orphan drug for AIDS wasting, the Office of Orphan Drug Development had previously designated ten other drugs, including the oral THC pill, the main active ingredient in marijuana, as Orphan Drugs for AIDS wasting.⁶¹² The FDA had even approved the oral THC pill for marketing for that indication.⁶¹³ By designating all these drugs as Orphan Drugs for the treatment of AIDS wasting syndrome, the Office had clearly accepted the claim that the disease, at the

⁶⁰⁷Sec. 5 (a) of the Orphan Drug Act. Grants and Contracts for Development of Drugs for Rare Diseases or Conditions. 21 U.S.C. 360ee.

⁶⁰⁸Sec. 525 of the Orphan Drug Act. Recommendations for Investigations of Drugs for Rare Diseases or Conditions.

⁶⁰⁹Sec. 527 of the Orphan Drug Act. Protection for Unpatented Drugs for Rare Diseases or Conditions.

⁶¹⁰Sec. 526 of the Orphan Drug Act. Designation of Drugs for Rare Diseases or Conditions. Designation occurs if "there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug."

⁶¹¹Sec. 5 (a) (2) Grants and Contracts for the Development of Drugs for Rare Diseases and Conditions.

The 200,000 patient threshold was added in 1984. This is not in the original 1983 law but was added later, see <http://www.fda.gov/opacom/laws/orphandg.htm>. According to Dr. Jack McCormick, Deputy Director, FDA Office of Orphan Product Development, personal communication April 15, 2000, since the 200,000 patient threshold was added in 1984, all but 1 or 2 drugs have been designed as Orphan Drugs through meeting the 200,000 threshold rather than through demonstrating that the costs of development cannot be recovered within the first seven years.

⁶¹²Among them were Marinol designated 1/15/91, Megace designated 4/13/88, Dihydrotestosterone designated 2/5/96, Oxandroline designated 9/06/91, Reduced L-glutathione designated 2/14/94, Sermorelin acetate designated 12/5/91, Somatropin (r-DNA) for injection designated 3/26/96, Somatropin for injection designated 11/15/91, testosterone designated 2/5/96, Thalidomide designated 3/11/96.

⁶¹³FDA approval of Marinol for AIDS Wasting took place on December 22, 1992. The approval was by the Division of Anti-Virals. The Office of Orphan Drug Development does not review or approve drugs but focuses first on determining whether drugs should be designated as Orphan Drugs and then on providing the Congressionally-authorized set of incentives for the development of orphan drugs.

time the sponsors sought designation for AIDS wasting, was under 200,000 per year. Since those designations had been made, the successful protease inhibitors had been introduced into AIDS treatment and had dramatically reduced the number of AIDS wasting patients. Furthermore, by approving the oral THC pill for marketing, FDA had accepted the claim that cannabinoids were beneficial in treating AIDS wasting.

From April 1997 to December 1998, the Office of Orphan Drug Development rejected three different revisions of the application to have smoked marijuana declared an Orphan Drug for AIDS wasting.⁶¹⁴ On September 22, 1997, however, the Office designated yet another drug as an Orphan Drug for AIDS-wasting.⁶¹⁵ Each time FDA's rejection was based on the claim that the population had not been convincingly demonstrated to be fewer than 200,000 per year. The main issue of contention was that, on the suggestion of clinicians who treated AIDS wasting patients, MAPS' application had defined AIDS wasting as the involuntary loss of 5% of body weight, instead of the 10% definition used by the Centers for Disease Control (CDC). Since increased mortality had been associated with an involuntary loss of 5% or more of body weight, in practice treatment was initiated before patients lost 10% of their body weight. But by shifting away from the CDC definition, there were no generally accepted estimates of the patient population. Although the clinicians were convinced that the total number of patients was still well under 200,000 per year, it was difficult to persuade FDA of this. The dramatic reduction of AIDS wasting cases due to the increased use of protease inhibitors made the struggle to prove the diminishing AIDS wasting population was fewer than 200,000 all the more frustrating.

The last communication from FDA was the most transparently political. Dr. Marlene Haffner, Director of the Office of Orphan Products Development, finally indicated that the population of AIDS wasting patients might indeed be fewer than 200,000 patients, but that marijuana might also be an effective treatment for cancer wasting patients, which might move the total number of patients back over the 200,000 per year limit.⁶¹⁶ When

⁶¹⁴Initial submission April 24, 1997 from Rick Doblin, President of MAPS, to FDA Office of Orphan Products Development. Revised submission Sept. 24, 1997 from Rick Doblin to FDA. Supporting letters to Office of Orphan Products Development of estimates of the population of AIDS wasting patients by Drs. Donald Abrams, Sept. 8, 1997, and Dr. Alice Tang, Oct. 10. 1997. Initial written rejection November 24, 1997 letter from Haffner, Marlene, Rear Admiral, United States Public Health Service, Director, FDA Office of Orphan Products Development to Rick Doblin, President, Multidisciplinary Association for Psychedelic Studies (MAPS). Second supporting letter by Dr. Alice Tang, March 18, 1998. Third revision submitted June 9, 1998 from Rick Doblin to FDA, supplemental submissions by Rick Dobin on August 25, 1998 and November 10, 1998. To review all the above documents, see <http://www.maps.org/mmj/odda/index.html>.

⁶¹⁵TheraDerm Testosterone Transdermal System designated September 22, 1997.

⁶¹⁶Haffner M. Director, FDA Office of Orphan Products Development. Letter to Rick Doblin, President, Multidisciplinary Association for Psychedelic Studies (MAPS). December 21, 1998.

FDA staff were pressed to explain why this logic hadn't stopped the Office of Orphan Drug Development from approving other drugs as orphan drugs for AIDS wasting, the verbal response was that the other approvals had been mistakes.⁶¹⁷ This conversation was followed up with a letter to FDA on February 19, 1999 asking for further clarification in writing of the exact problem as perceived by FDA.⁶¹⁸ Almost two years had passed seeking a designation that eleven other drugs had already obtained, for a disease that was rapidly disappearing.

Psychedelic Research- FDA Says Wait

As psychedelic researchers in the United States sought to move beyond basic Phase I safety studies, they encountered unexpected resistance from the DACCADP. In October 1997, Drs. Kurland, Yensen, Dryer had legally imported LSD from Switzerland for use in their FDA-approved study of LSD-assisted psychotherapy in the treatment of substance abusers. Before the study actually started, DACCADP placed a Clinical Hold on the study, citing new concerns over protocol design issues.⁶¹⁹

Meanwhile, by mid-1997, Dr. Grob had completed the data analysis of his Phase I safety study. He subsequently contacted FDA to discuss his intention to submit a new protocol to investigate the use of MDMA in the treatment of cancer patients. This study had already been reviewed in 1992 by FDA's Drug Abuse Advisory Committee, which recommended that a basic Phase I safety study be conducted first with the cancer patient study following if the Phase I study did not generate data suggesting too great a risk to the patients.⁶²⁰ Rather than welcome the cancer patient protocol, DACCADP requested that Dr. Grob submit the protocol informally.⁶²¹

In August 1997, Dr. Grob submitted the first draft of the cancer patient protocol for informal review. On February 25, 1998, after Dr. Grob had waited six months for a

<http://www.maps.org/mmj/odda/12219801.html>

⁶¹⁷personal communication between FDA staff and Rick Doblin, December 1998.

⁶¹⁸Doblin R. Letter to Dr. Marlene Haffner, Director, FDA Office of Orphan Products Development. February 19, 1999. <http://www.maps.org/mmj/odda/021699.html>

⁶¹⁹McCormick C. Director of FDA's Division of Anesthetics, Critical Care and Addiction Drug Products. Letter to Richard Yensen, Ph.D. regarding IND #3250. October 28, 1997. Dr. McCormick's letter placed Dr. Yensen's substance abuse protocol on Clinical Hold, prior to the time that any patients had been treated. The letter also reminded the investigators that the cancer patient protocol had been placed on hold in 1986, though Dr. Kurland had no record of receiving any notification of that Clinical Hold.

⁶²⁰Ironically, the one person who had a negative psychological panic reaction during the experimental procedure was later determined to have been administered the placebo. Personal communication, Dr. Grob, August 30, 1999.

⁶²¹Grob C. Letter to Rick Doblin. March 15, 1999. Dr. Grob's letter was submitted to FDA Ombudsman Jim Morrison.

response to the informal submission of his MDMA/cancer patient protocol, FDA arranged a teleconference with Dr. Grob at which he was finally given a verbal critique of his protocol design.⁶²² By July 1998, Dr. Grob had modified the protocol according to the guidance he had been given during the teleconference and submitted another draft of his MDMA protocol to FDA, once again doing so informally at the request of the DAACCDP.⁶²³

Dr. Grob didn't hear from FDA until March 1999, nine months after he had submitted his protocol for informal review. From his perspective, the news from FDA was worse than the wait. Dr. Grob was informed that the entire concept of studying MDMA in humans had been rejected until additional preclinical animal studies were conducted.⁶²⁴ FDA delays in responding to Dr. Grob's submissions harkened back to the way psychedelic research protocols had been treated when the responsibility for their review was under the jurisdiction of Dr. Leber in the Division of Neuropharmacological Drug Products.

Some Studies Approved

Not all the decisions of DACCADP during this period were restrictive. A pilot study into the therapeutic use of psilocybin in obsessive/compulsive patients was approved in September 1998, though put on hold until a source of psilocybin could be arranged.⁶²⁵ In addition, two new NIDA-funded non-therapeutic human studies with Schedule I drugs were approved by DACCADP. One such study is investigating the use of mescaline in PET brain imaging studies,⁶²⁶ while the other involves the administration of heroin to addicts along with drugs designed to block the effects of heroin.⁶²⁷

September 1998 Senate Confirmation Hearings For New FDA Commissioner

On Sept. 2, 1998, about a year and a half after Dr. Kessler had resigned as FDA Commissioner, Senate confirmation hearings were held with Dr. Jane Henney, nominated by the Clinton administration to be the new FDA Commissioner. Dr. Henney had served under Dr. Kessler as the Deputy Commissioner for Operations at FDA from 1992 to 1994,

⁶²²Dr. Grob's written notes of FDA teleconference, February 25, 1998.

⁶²³Dr. Grob's FDA submissions took place on July 15 and July 24, 1998.

⁶²⁴McCormick C. Director of FDA's Division of Anesthetics, Critical Care and Addiction Drug Products. Letter to Dr. Grob. March 18, 1999.

⁶²⁵IND # 56,530. McCormick C. Director of FDA's Division of Anesthetics, Critical Care and Addiction Drug Products. Letter to Dr. Francisco Moreno. Sept 17, 1998. Dr. Moreno spent over a year trying to obtain the psilocybin from NIDA, without success. MAPS has located an alternative source, Organix Pharmaceuticals.

⁶²⁶The principal investigator on this study is Dr. Roy Matthew, Duke University.

⁶²⁷Wren C. In the Battle Against Heroin, Scientists Enlist Heroin. Science Times- New York Times. June 6, 1999: D1. The principal investigator on this study is Dr. Herb Kleber, NY State Psychiatric Institute.

during the time of Pilot Drug's existence. Dr. Henney had paid close attention to the NDA Day innovations at Pilot Drug, and had expressed her support for that and other innovations being tested by Pilot Drug.⁶²⁸

During her confirmation hearings, Dr. Henney was questioned about her involvement in FDA's proactive support of research with RU-486, the abortion pill. She was also questioned about her position concerning FDA regulation of tobacco. There was no questioning regarding FDA's approval of psychedelic or medical marijuana research, suggesting that at that time there was probably little or no direct Congressional pressure being placed on FDA to restrain psychedelic or medical marijuana research.⁶²⁹

In November 1998, Dr. Jane Henney was sworn in as the new FDA Commissioner.

Congress and Medical Marijuana

A Sense of Congress resolution in October 1998 endorsed the FDA-regulated scientific process as the proper method of determining the medical use of marijuana and objected to the use of state medical marijuana initiatives for this purpose.⁶³⁰ While Congressional proponents of medical marijuana had filed a bill to reschedule marijuana in order to make it available as a prescription medicine without additional research,⁶³¹ and opponents had filed a bill seeking to forbid the expenditure of any federal money on research into marijuana's medical uses,⁶³² neither of these bills received enough support

⁶²⁸Dr. Peck gave me a copy of Dr. Loren Miller's paper on Pilot Drug's NDA Day innovation, to be discussed in Chapter 3. Dr. Henney had handwritten her comments to Dr. Peck on the first page of the paper. The note says, "Carl P- Thanks- I enjoyed reading this very much-It speaks well of the kind of innovative management that CDER enjoys!... The process sounds and paper reads like a spy thriller!!! Jane H."

⁶²⁹Confirmation of Jane E. Henney to be Commissioner of the Federal Food and Drug Administration, Senator James Jeffords (R-VT). Hearing of the Senate Labor and Human Resources Committee, September 2, 1998.

⁶³⁰Omnibus Consolidated and Emergency Supplemental Appropriations Act of 1999. 105 P.L. 277; 1998 Enacted H.R. 4328; 105 Enacted H.R. 4328. October 19, 1998. Divison F- Not Legalizing Marijuana For Medical Use (11) Congress continues to support the existing Federal legal process for determining the safety and efficacy of drugs and opposes efforts to circumvent this process by legalizing marijuana, and other Schedule I drugs, for medicinal use without valid scientific evidence and the approval of the Food and Drug Administration; and (12) not later than 90 days after the date of the enactment of this Act...(B) the Commissioner of Foods and Drugs shall submit to the Committee on Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate a report on the specific efforts underway to enforce sections 304 and 505 of the Federal Food, Drug, and Cosmetic Act with respect to marijuana and other Schedule I drugs.

⁶³¹H.R. 1782 Medical Use of Marijuana Act.

for any action to be taken on them.⁶³³

Congress did pass one medical marijuana bill, sponsored by Rep. Bob Barr (R-GA) preventing the Washington, D.C. government from counting the ballots⁶³⁴ from a November 1998 medical marijuana initiative.⁶³⁵ This is the only instance in the history of the United States in which the voters in a legally-constituted election were prevented from learning the outcome of their votes. After litigation, the DC Court of Appeals ruled on September 17, 1999 that the Barr Amendment was unconstitutional and ordered the ballots counted.⁶³⁶ The results were 69% in favor of the medical marijuana initiative. Congress responded by passing another bill that prevented the D.C. government from implementing the initiative.⁶³⁷ One of the main arguments made in Congress, that decisions about the medical use of marijuana should be based on scientific research rather than decided at the ballot box, provides rhetorical support for the conduct of FDA-approved research and insulates FDA somewhat from criticism for approving research protocols.

In the legal arena, the Federal Court of Appeals (9th Circuit, covering Northern California) has expressed some support for the validity of the medical necessity defense as it applies to the medical use of marijuana under California Proposition 215, the Compassionate Use Act.⁶³⁸

⁶³²H.R.1469, withdrawn by unanimous consent.

⁶³³Randall IV B. *Medical Use of Marijuana: Policy and Regulatory Issues*. Congressional Research Service Report for Congress. July 26, 1999. Order Code RL30274.

⁶³⁴Barr Amendment §171. District of Columbia Appropriations Act. Omnibus Consolidated Appropriations Bill of 1999. 105 P.L. 277, 112 Stat. 2681-150. October 21, 1998.

⁶³⁵On November 3, 1998, the citizens of Washington, DC voted on Initiative 59, also known as The Legalization of Marijuana for Medical Treatment Initiative of 1998.

⁶³⁶Turner v. D.C. Board of Elections & Ethics, 77 F. Supp. 2d 25 (D.D.C. 1999). “[T]he Court holds that the phrase “conduct any ballot initiative” in the Barr Amendment does not prevent the District of Columbia Board of Elections and Ethics from counting, releasing and certifying the vote on Initiative 59 taken on November 3, 1998... The issue here is whether Congress’s plenary power over the District of Columbia encompasses the power to prevent political speech, in the form of the results of votes properly cast in a properly conducted ballot referendum, from being made public. The answer to that question must be no.

⁶³⁷Congress passed a bill that included a provision prohibiting Initiative 59 from coming into effect. District of Columbia Appropriations. PL 106-113 [H.R. 3194], 113 Stat. 1501; Sec. 167 (b). November 29, 1999.

⁶³⁸United States v. Oakland Cannabis Buyers’ Cooperative, 190 F. 3rd 1109 (9th Cir. 1999). The decision, dated Sept. 13, 1999, stated, “In particular, the district court is instructed to consider, in light of our decision in United States v. Aguilar, 883 F. 2nd 662, 692 (9th Cir. 1989), the criteria for a medical necessity exemption, and, should it modify the injunction, to set forth those criteria in the modification order.” On February 29, 2000, the 9th Circuit Court of Appeals refused to consider an appeal for rehearing and rehearing en banc that had been requested by Clinton Administration Attorney General Janet Reno,

New Guidelines for Research in Patients with Mental Illness

On January 9, 1999, the National Bioethics Advisory Commission (NBAC) issued a report on the need for new regulatory protections for research subjects suffering from mental disorders. The concern is that mental disorders could affect people's decisionmaking capacity, hence limiting their ability to understand fully the risks they would incur as subjects in a specific research study, thereby compromising their ability to give informed consent.⁶³⁹ Among the catalysts for the NBAC report were negative publicity and lawsuits that several NIMH-funded researchers had attracted as a result of studies in which ketamine, an FDA-approved prescription medicine approved for use as a dissociative anesthetic in medical operations, was administered to schizophrenics.⁶⁴⁰ In lower doses, ketamine has been found to have psychedelic effects.

The type of research study in which ketamine was administered to schizophrenics was called a pharmacologic challenge test. These are tests designed to probe the neurochemical basis of mental disease by measuring the patients' psychological and physiological responses to the test, or challenge, drug. Subjects with a brain chemistry within the normal range will react one way to ketamine, while subjects whose brain chemistry is outside the normal range will react differently. In these studies, ketamine was administered without direct therapeutic intent. To the contrary, the explicit aim of the research was to determine if ketamine would temporarily increase the schizophrenic symptoms of the subjects. In one instance, a subject was taken off his normal medication only to commit suicide after participating in the research study.⁶⁴¹

In addition to being useful as a chemical agent in pharmacologic challenge testing,

According to the order, "the full court was advised of the petition for rehearing en banc and no judge of the court has requested a vote on the petition for rehearing en banc." (D.C. No. C 98-00088-CRB, Nos. 98-16950, 98-17044, 98-17137, Judges Schroeder, Reinhardt and Silverman). See also United States v. Smith, No. 99-10477 (9th Cir. 2000). According to a Feb., 2000 press release from David Michael, B.E. Smith's attorney, "B.E. Smith will be the first criminal defendant in this country who has federal court permission to manufacture marijuana and distribute it to sick and dying individuals without fear of federal prosecution, and who can do so while he is on appeal from his own criminal conviction for that very conduct."

⁶³⁹Research Involving Persons with Mental Disorders that May Affect Decisionmaking Capacity. Report and Recommendations of the National Bioethics Advisory Commission. December 1, 1998: NIMH. Rockville, MD.

⁶⁴⁰Kong D. Mental Health Body Will Review Tests-Decision Follows a Series of Reports. *Boston Globe* January 22, 1999: A20.

⁶⁴¹Whitaker R, Kong D. Testing Takes Human Toll. *Boston Globe* November 15, 1998. Kong D. Panel Urges Review of Patient Studies. *Boston Globe* November 18, 1999. Kong D. Drug Studies Are Questioned. *Boston Globe* December 31, 1999.

ketamine-assisted psychotherapy has been used successfully in Russia as an adjunct to psychotherapy in the treatment of alcoholics⁶⁴² and heroin addicts.⁶⁴³

On January 20, 1999 Dr. Steve Hyman, Director of the National Institute of Mental Health (NIMH), announced that NIMH was going to establish a special national safety review panel to evaluate "risky" research protocols either funded by NIMH grants or conducted intramurally. This review group would be in addition to the standard NIMH grant review process, local IRB oversight, and the FDA protocol review process. What constitutes a risky study was "undefined but clearly would include the kind of work that got negative publicity in 1998: studies that halt mental patients' ongoing medication, replace it with a placebo, or "challenge" them by exposing them to chemicals that intensify their symptoms. It would balance scientific objectives with human risks"⁶⁴⁴ Dr. Hyman reported that he had convened an ad hoc panel of twenty outside scientists on December 8-9, 1998 to review all NIMH intramural research, in order "to get our house in order."⁶⁴⁵

Since psychedelic psychotherapy research in patient populations can be considered to exacerbate symptoms,⁶⁴⁶ if only temporarily, these new regulations governing research with patients suffering from mental illness may eventually apply to some psychedelic research protocols. Though it seems unlikely that NIMH would actually fund psychedelic psychotherapy studies at this time,⁶⁴⁷ it is possible that the FDA could decide to adopt these guidelines for all psychedelic research projects.

The primary issues for review by the NBAC and the NIMH ad hoc committee were whether the risks of the research were fully communicated to the subjects, whether subjects with mental illness (diminished decisionmaking capacity) had the ability to give informed consent even if the risks were adequately communicated and whether the information to be gained by the research was worth the risks.

Harold Shapiro, Chair of the NBAC and President of Princeton University, explained, "In this report, NBAC considers how ethically acceptable research can be

⁶⁴²Krupitsky E, Grinenko A. Ketamine Psychedelic Therapy (KPT): A Review of the results of ten years of research. *J Psychoact Drug* 29 (1997) 2:165-183.

⁶⁴³Krupitsky E, Burakov A, Romanova T, Strassman R, Grinenko A. Ketamine-Assisted Psychotherapy (KPT) of Heroin Addiction: Immediate Effects and Six Months Follow-up. *BullMAPS* 9 (1999) 4:21-26. <http://www.maps.org/news-letters/v09n4/09421kru.html>

⁶⁴⁴Marshall E. NIMH to Screen Studies for Science and Human Risks. *Science* 283 (Jan 22, 1999) 5401: 464.

⁶⁴⁵Ibid., 465.

⁶⁴⁶Symptom exacerbation studies have been considered to include "behavioral flooding in phobic disorders research," a processs that generates psychological effects similar to those generated by psychedelics.

Carpenter W. The Schizophrenia Ketamine Challenge Study Debate. *Biol Psychiat* 46 (1999): 1081-1091.

⁶⁴⁷personal communication, Dr. David Shore, Associate Director for Clinical Research, National Institute for Mental Health, March 3, 2000.

conducted with human subjects who suffer from mental disorders that may affect their decisionmaking capacity; whether additional protections are needed; and if so, what they should be and how they should be implemented... Although existing federal regulations for research involving human subjects have provided special protections for certain populations that are regarded as particularly vulnerable, persons with mental disorders who may have impaired capacity to make decisions, and therefore give voluntary informed consent, have not received any such protections. We believe that this state of affairs is not satisfactory, and that additional federal protections are needed.”⁶⁴⁸ Recommendations for new regulations and procedures centered around six sections related to: “review bodies; research design; informed consent and capacity; categories of research; surrogate decision making; and education, research, and support.”⁶⁴⁹ The report recommended that non-therapeutic studies involving greater than minimal risk could be conducted in patients with impaired decisionmaking ability only under strictly limited conditions.⁶⁵⁰

New Guidelines Applied to MDMA Research

Even though the NBAC report was focused on research in subjects with major mental illnesses such as schizophrenia and psychosis, it can be a valuable exercise to apply the analysis and recommendations of the NBAC’s report to the design and conduct of psychedelic research studies. In fact, elements of the NBAC report have already been explicitly used as guidelines by two co-authors of an editorial in a respected scientific journal. The co-authors, Dr. Jeffrey Lieberman and Dr. George Aghajanian, reviewed the risks of MDMA research in MDMA-naïve healthy subjects.⁶⁵¹ What makes this editorial especially influential is that one of its co-authors, Dr. Lieberman, was co-chair of the NIMH ad hoc committee that reviewed all of NIMH’s intramural studies. In evaluating the ethics of MDMA research, Dr. Lieberman seems to have considered the administration of MDMA as a sort of pharmacologic challenge test, probably due to MDMA’s known impact as a compound that triggers the release of the neurotransmitter serotonin, as well as dopamine and to a certain extent other neurotransmitters as well.. Though this conception is overly reductionistic when it comes to characterizing the subjective nature of the MDMA

⁶⁴⁸Shapiro H. Chair of the National Bioethics Advisory Commission. Letter of Transmittal to the President. January 9, 1999. Research Involving Persons with Mental Disorders that May Affect Decisionmaking Capacity. Report and Recommendations of the National Bioethics Advisory Commission. December 1, 1998: NIMH. Rockville, MD.

⁶⁴⁹Executive Summary, Research Involving Persons with Mental Disorders that May Affect Decisionmaking Capacity. Report and Recommendations of the National Bioethics Advisory Commission. December 1, 1998: NIMH. Rockville, MD.

⁶⁵⁰Ibid., Chapter 5, Recommendation 12.

⁶⁵¹Lieberman J and Aghajanian G. Editorial—Caveat Emptor: Researcher Beware. *Neuropsychopharm* 21 (1999) 4:471-473.

experience, it can be helpful in evaluating the physiological risks associated with the administration of MDMA to human subjects.

The editorial by Dr. Lieberman and Dr. Aghajanian was based on a heated exchange about the risks of MDMA research as debated in two articles in the same issue of the journal. The first article was by a group of Dutch physicians at the Center for Human Drug Research, Leiden, who opposed MDMA research in healthy volunteers. They specifically objected to a Swiss study in MDMA-naïve subjects that had been published in a previous issue of the journal.⁶⁵² The Dutch physicians asserted that the risk of MDMA neurotoxicity was so great that “It is undesirable that illicit drugs that are neurotoxic in animal experiments are administered to healthy volunteers, even though people take these drugs voluntarily for recreational purposes.”⁶⁵³ In response, the Swiss team that conducted the original research asserted that the scientific evidence suggested that it was unlikely that the doses of MDMA employed in their research would cause any MDMA-related neurotoxicity, and that there were substantial offsetting benefits of the research.⁶⁵⁴ These benefits included “objective, scientific information about the full range of effects of MDMA that can be used to shed light on the causes and consequences of the non-medical use of MDMA by millions of people around the world....research into the mechanism of action of MDMA in normals should provide insight into pathophysiological processes underlying psychiatric disorders...normative data obtained with MDMA in normals should also be useful to interpret psychological and neuropsychological data obtained in MDMA users.”⁶⁵⁵

Another argument in favor of the use of MDMA-naïve subjects, though not stated by the Swiss researchers, is that studies in healthy MDMA-naïve volunteers can generate data that can be used to evaluate risk/benefit ratios for subsequent studies of the therapeutic potential of MDMA-assisted psychotherapy in patient populations. Research with patient populations is likely to involve at least some and perhaps all MDMA-naïve subjects.

The editorial commenting on the exchange raised three separate issues that had been reviewed by the NBAC report; the issue of informed consent; the risk that the procedure (the administration of MDMA) can cause harm to the subjects; and “whether the quality and importance of the scientific information to be gained justifies the use of research designs that carry more than minimal risk and are viewed as controversial.”⁶⁵⁶ Drs.

⁶⁵²Vollenweider F, Gamma A, Liechti M, Huber T. Psychological and cardiovascular effects and short-term sequelae of MDMA (Ecstasy) in MDMA-naïve healthy volunteers. *Neuropsychopharm*19 (1998) 4:241-251.

⁶⁵³Gilsman G, Vrekes R, van Gerven J, Cohen A. MDMA Study. *Neuropsychopharm*21 (1999) 4:597.

⁶⁵⁴Vollenweider F, Gamma A, Liechti M, Huber T. Is A Single Dose of MDMA Harmless?

*Neuropsychopharm*21 (1999) 4:598-600.

⁶⁵⁵Ibid., 599.

⁶⁵⁶Lieberman J, Aghajanian G. (1999):472.

Lieberman and Aghajanian concluded that the evidence demonstrated that the healthy volunteers in the Swiss study “were competent to provide informed consent and procedural standards appear to have been met...the evidence did not support the view that single oral doses of 1.7 mg/kg of MDMA... are likely to produce damage to serotonin terminals...it [MDMA] seems to have been on the whole pleasurable and it did not cause severe distress or any untoward behavioral reactions...the study of Vollenweider and colleagues (1998) was... safe and appropriate.”⁶⁵⁷ The one additional risk that was noted was the uncertain likelihood that MDMA-naive subjects might be tempted to become MDMA abusers as a result of being exposed to the drug for the first time in the research study. Given the current state of knowledge, Drs. Lieberman and Aghajanian stated that “it is imperative that this issue is described as a potential risk in the informed consent process.”⁶⁵⁸

As a result of data gathered in ongoing studies in MDMA-naive subjects, such as the Swiss experiment, risk estimates will be more accurate for studies involving MDMA-naive patient populations. For studies of MDMA and other psychedelics in patient populations, for example in subjects suffering from depression and anxiety due to terminal illness or post-traumatic stress disorder (PTSD), the critical ethical issues will revolve around assessing the ability of the patients to understand the risks of the treatment and offer free and full informed consent, then balancing the risks with possible therapeutic benefits. Strong legal arguments have also been made that terminally ill patients, like patients with mental disorders, are from vulnerable populations and deserve increased safeguards to protect them from being unduly swayed as a result of being in “desperate need for a cure.”⁶⁵⁹ Though not entirely certain, it still seems possible to design a psychedelic psychotherapy pilot study so that whatever protections for research subjects that IRBs and government regulatory agencies think should be provided can indeed be provided.⁶⁶⁰

Safety of Psychedelic Research

Dr. Wright believes that the change in attitudes at FDA toward psychedelic and marijuana research after the end of Pilot Drug, and his departure from the FDA, was not due to problems generated by the studies that did take place. From his perspective, the careful review of the design of the psychedelic protocols conducted by FDA staff helped

⁶⁵⁷Ibid., 472.

⁶⁵⁸Ibid., 472.

⁶⁵⁹Addicott D. Regulating Research on the Terminally Ill: A Proposal for Heightened Safeguards. *J Contemp Health Law Pol* 15 (1999) 2:479-524.

⁶⁶⁰An entire issue of Biological Psychiatry was devoted to articles about the NBAC report and ethical aspects of protocol design, informed consent, and IRB review of psychiatric research in the study of mental illness. Biological Psychiatry 46 (October 15, 1999) 8:1007-1119. The American College of Neuropharmacology (ACNP) is also developing guidelines for drug and symptom provocation studies, with expected completion sometime in 2000.

introduce important safety monitoring to the protocols so as to ensure minimization of risk. Dr. Wright stated, “without peer review of INDs by FDA, accidents would have happened.”⁶⁶¹ He mentioned the monitoring of blood pressure and pulse as simple additions to protocols that FDA insisted upon. He knew of no reports from any of the studies of serious adverse events experienced by any of the subjects. Furthermore, the studies generated valuable scientific data that resulted in numerous publications. Dr. Wright also felt that FDA IND review and approval probably helped Institutional Review Boards (IRBs) to develop courage to approve controversial protocols.

According to Dr. Wright, nothing in the data suggested that FDA should change its policy to one in which research was considered too risky to proceed. Dr. Wright commented “nobody was permanently harmed, harms to subjects were minimized. It was a sensible policy.”⁶⁶²

A Formal Inquiry

In Spring 1999, a series of formal complaints regarding bureaucratic obstacles to MDMA and medical marijuana research were lodged by Dr. Grob and Dr. Russo, with the assistance of this author, with Mr. Jim Morrison, FDA’s CDER Ombudsman. These complaints were intended to help Dr. Grob and Dr. Russo determine why permission for their research had not been obtained and whether there was any way to resolve FDA concerns so that research could move forward again. They wondered whether the dissolution of Pilot Drug and the departure of Dr. Wright indicated the end of a brief period of time in which researchers interested in conducting human clinical research into the therapeutic potentials of psychedelics and marijuana had a reasonable chance of obtaining FDA permission for their studies.

Mr. Morrison’s inquiry into Dr. Russo’s complaint took place at a time when powerful external political pressure to support medical marijuana research had been generated by the passage of eight state medical marijuana initiatives.⁶⁶³ Dr. Russo’s complaint was made even stronger by the March 17, 1999 release of the Institute of Medicine’s report on medical marijuana, which contained the recommendation that FDA-approved research into the medical use of marijuana be conducted.⁶⁶⁴ The release of the IOM report was front page news in the Washington Post, New York Times and USA Today, and coincided with the day that this author met in person with Mr. Morrison at his office.⁶⁶⁵ The purpose of the meeting was to discuss Dr. Russo’s request to have his

⁶⁶¹personal communication, Dr. Wright, March 8, 1999.

⁶⁶²personal communication, Dr. Wright, March 8, 1999.

⁶⁶³California and Arizona in 1996; Alaska, Washington State, Oregon, Washington, DC, Nevada and Arizona a second time in 1998. Maine passed a medical marijuana initiative in 1999.

⁶⁶⁴At a cost of almost two years and \$1 million, the IOM report came to essentially the same conclusions as NIH’s Workshop on the Medical Utility of Marijuana, at a cost of about six weeks and relatively little money.

protocol reviewed by FDA, Dr. Grob's request to obtain feedback from Dr. McCormick concerning his protocol for MDMA-assisted psychotherapy in the treatment of anxiety and depression in cancer patients, and to inquire whether there was some way to move forward with the application to have marijuana declared an Orphan Drug for AIDS wasting.

Dr. Morrison indicated that Dr. Janet Woodcock and Dr. Robert Temple, the senior FDA officials with whom he had discussed the complaints, both reiterated their support of FDA's policy of permitting research with drugs of abuse to be conducted, as long as the studies were scientifically rigorous and the risk/benefit ratio had been carefully considered. Mr. Morrison listened carefully and seemed concerned that standard FDA procedures may not have been followed in the review Division. He promised to make additional inquiries and get back in touch with Drs. Russo and Grob in the near future. He also indicated he would refer the matter of the Orphan Drug application to a different Ombudsman who worked with that Office.

Outcome of Ombudsman's Review

On May 25, 1999, FDA's Office of Orphan Drug Development designated marijuana an Orphan Drug for AIDS wasting, after five previous rejections.⁶⁶⁶ ⁶⁶⁷ The inquiry by the FDA Ombudsman with authority to review decisions in the Office of Orphan Product Development may have contributed to this decision.

On June 24, 1999, the Ombudsman's inquiries culminated in a decision by the DACCADP to permit Dr. Grob to conduct research with MDMA in cancer patients, with final protocol design still to be negotiated.⁶⁶⁸ No preclinical studies need to be conducted in animals and no additional studies in healthy subjects will be required prior to the implementation of a pilot study in cancer patients. Though there are still important issues involving dose levels, patient characteristics and outcome measures that can only be resolved during the protocol development and review process, the likelihood that a mutually satisfactory design will emerge seems strong.

According to Mr. Morrison, standard FDA policy is that FDA has an obligation to uphold prior commitments, especially in the absence of new information suggesting that keeping such commitments would not be in the public's interest. By this logic, the recommendation of the 1992 Drug Abuse Advisory Committee that Dr. Grob first conduct

⁶⁶⁵Joy J, Watson S, Benson J (eds.): *Marijuana and Medicine: Assessing the Science Base*. Washington, DC: Institute of Medicine, National Academy Press, 1999. <http://stills.nap.edu/books/0309071550/html>

⁶⁶⁶Haffner M. Director, FDA Office of Orphan Products Development. Letter to Rick Doblin. President, Multidisciplinary Association for Psychedelic Studies (MAPS). May 25, 1999.

⁶⁶⁷Buday P. Hints on Preparing Successful Orphan Drug Designation Requests. *Food Drug Law J* 51 (1996) 1:75-84.

⁶⁶⁸McCormick C. Director of FDA Division of Anesthetics, Critical Care and Addiction Drug Products. Letter to Dr. Charlie Grob. July 23, 1999. The letter summarized the FDA teleconference of June 24, 1999.

a Phase I MDMA safety study in healthy normals before moving directly to a study in cancer patients created a prior commitment that the FDA needed to try to honor. This recommendation was strengthened by virtue of the fact that Dr. Grob's Phase I study generated data that supported the view that MDMA could be safely administered within the context of clinical research, though as previously discussed MDMA was only administered to MDMA-experienced subjects.

Another positive outcome of the Ombudsman's review took place in June 1999, when Dr. Russo was encouraged to submit his marijuana protocol to FDA for formal review. Dr. Russo's protocol was subsequently approved by FDA on September 17, 1999 but placed on Clinical Hold pending resolution of the supply issue.⁶⁶⁹ According to Mr. Morrison, standard FDA procedures do permit INDs to be reviewed in sections, allowing the review of protocol designs to proceed separate from the review of the chemistry and manufacturing data for the drug to be used in the study.⁶⁷⁰ No special exceptions to the rules were needed for Dr. McCormick to review Dr. Russo's protocol while efforts to obtain marijuana from NIDA were still in process. On the contrary, it was Dr. McCormick's refusal to review the protocol that was the exception to standard FDA policy.

HHS Guidelines for Provision of Marijuana for Research.

On May 21, 1999, HHS released its new guidelines for scientists seeking to obtain supplies of marijuana from NIDA for use in research into the medical uses of marijuana.⁶⁷¹ These guidelines, which were to become effective December 1, 1999, stated that NIDA would provide marijuana to privately-funded research projects as well as to government-funded projects. The guidelines stated, "To facilitate research on the potential medical uses of cannabinoids, HHS has determined that it will make research-grade marijuana available on a cost-reimbursable basis, subject to the priorities and conditions described in section III, below."⁶⁷² In Section III, the HHS guidelines stated, "After submission, the scientific merits of each protocol will be evaluated through a Public Health Service interdisciplinary review process...In addition, researchers who propose to conduct investigations in humans must be able to fulfill the Food and Drug Administration's investigational new drug (IND) requirements and must obtain a valid registration from the Drug Enforcement Administration (DEA) for research with Schedule I drugs."⁶⁷³

In contradiction to the recommendations of NIH's Expert Committee on the

⁶⁶⁹McCormick C. Director of FDA Division of Anesthetics, Critical Care and Addiction Drug Products. Letter to Dr. Ethan Russo. Sept. 21, 1999. Re: IND #58,177.

⁶⁷⁰personal communication, Jim Morrison, March 17, 1999.

⁶⁷¹Guidance On Procedures for the Provision of Marijuana for Medical Research. Department of Health and Human Services. May 21, 1999. <http://www.mpp.org/hhsguide.html>

⁶⁷²Ibid., Section II. Availability of Marijuana for Research Purposes.

⁶⁷³Ibid., Section III. Elements for Considering Proposed Studies.

Medical Utility of Marijuana, the HHS guidelines specified that FDA approval of a protocol would not be sufficient to ensure a supply of marijuana for a study. A Public Health Service review would also be required to evaluate the “scientific merits” of the protocol. Yet according to FDA’s Dr. Robert Temple, director of the Office of Drug Evaluation I, in FDA’s Center for Drug Evaluation and Research (CDER), the role of the FDA is precisely to review the scientific merit of protocols when requested by pharmaceutical companies or individual researchers planning major studies to determine a drugs’ efficacy and safety profile. As Temple notes: “We try to find and eliminate flaws in the individual studies and overall development plan that we know will give us trouble later on in the NDA review. We don’t want people to carry out a large study that has no chance of being considered adequate and well-controlled.”⁶⁷⁴ Due to the HHS guidelines and NIDA’s monopoly on the supply of marijuana for FDA-approved research, marijuana is the only Schedule I drug for which FDA approval of a protocol needs to be supplemented by yet another government-supervised review, even for privately-funded projects.

The HHS guidelines did endorse the recommendations of the NIH Expert Committee when it came to protocol design. The HHS guidelines stated, “A clinical study involving marijuana should include certain core elements, many of which reflect recommendations made by the 1997 NIH Workshop. A study that incorporates the NIH Workshop recommendations will be expected to yield useful data and therefore, will be more likely to be eligible to receive marijuana under the HHS program.”⁶⁷⁵ Whether any protocol will be approved by this NIDA/PHS review process remains to be determined.

Testing the Guidelines

On December 1, 1999, Dr. Russo’s protocol, approved by the FDA and designed in accordance with the core elements recommended by the 1997 NIH Workshop, became the first protocol to come up for review by an NIDA/PHS committee, in accordance with the new HHS guidelines. According to a senior NIDA official, Dr. Russo’s protocol was judged to be inadequate and was rejected.⁶⁷⁶ The basis for the rejection by the NIDA/PHS committee was explained in a letter sent to Dr. Russo on February 1, 2000.⁶⁷⁷

The second test of the HHS guidelines came from a research proposal submitted for review in December 1999 by San Mateo County Health Department, for a \$350,000 study of AIDS and cancer patients funded by San Mateo County.⁶⁷⁸ Political support for medical

⁶⁷⁴Farley D. Benefit Vs. Risk: How FDA Approves New Drugs. *FDA Consum*(Special Report), January 1995. <http://www.fda.gov/fdac/special/newdrug/benefits.html>

⁶⁷⁵Guidance On Procedures for the Provision of Marijuana for Medical Research. Section IV. Marijuana Trial Design Elements.

⁶⁷⁶Gust S. E-mail message to Dr. Russo. December 6, 1999.

⁶⁷⁷Mann L. Public Health Service, Center for Scientific Review. Summary Statement: Cannabis in Acute Migraine Treatment Project. Letter to Dr. Russo. February 1, 2000.

<http://www.maps.org/mmj/russo1199/02010001.html>

marijuana research was provided by a bipartisan group of 34 members of Congress, coordinated by Rep. Anna Eshoo, D-Palo Alto, in the form of a letter sent to Health and Human Services Secretary Donna Shalala urging her to support such projects.⁶⁷⁹ In order to make approval more likely, San Mateo County officials purposely decided not to submit an application for permission to conduct a study of marijuana's efficacy but decided instead to seek approval for a study that would simply determine the feasibility of conducting subsequent efficacy studies.⁶⁸⁰ The study that was submitted was for a 45-day study of the use of marijuana in HIV-related neuropathy (pain). It was designed to determine whether subject retention would be sufficient and whether the subjects would refrain from supplementing the marijuana they received as part of the study with supplies obtained from other sources. On May 15, 2000, after waiting about six months, San Mateo County officials received word that their proposal would be approved with one problematic condition that could sabotage the study.⁶⁸¹ The HHS review committee indicated that the risk of diversion was so great that subjects would need to be restricted to five marijuana cigarettes per visit. Since the subjects were expected to use three marijuana cigarettes per day, this requirement would have them coming back to the Health Department more frequently than once every other day. This is a rather heavy burden for people trying to lead a normal life and could impact subject retention. The idea that diversion was likely to be a significant problem is debatable, since the potency of the marijuana cigarettes supplied by NIDA is so low as to be only 20-25% of that easily available to patients from other sources.⁶⁸² The HHS committee also seemed to ignore the fact that the eight patients who already receive marijuana from NIDA as part of the Compassionate IND program receive their supply in tins containing 300 cigarettes at a time.⁶⁸³ San Mateo County officials intend to negotiate with the HHS review committee to obtain approval to give patients a one week supply.⁶⁸⁴ FDA and DEA approval for the study must still be obtained.

Understanding Internal FDA Dynamics

⁶⁷⁸Gathright A. Federal OK Needed: San Mateo County Plans Medicinal Marijuana Trial. *San Jose Mercury News*December 26, 1999.

⁶⁷⁹35 Members of Congress. Letter to HHS Secretary Donna Shalala. November 30, 1999.

<http://www.mpp.org/guidelines/ltr2.html>

⁶⁸⁰personal communication, Dr. Scott Morrow, San Mateo County Health Department, May 16, 2000.

⁶⁸¹Guido M. Medical pot study receives support. *San Jose Mercury News*May 16, 2000.

⁶⁸²Gieringer D. Medical Cannabis Potency Testing Project. *Bull MAPS* 9 (Autumn 1999) 3:20-22.
<http://www.maps.org/news-letters/v09n3/09320gie.html>

⁶⁸³Randall R, O'Leary A. *Marijuana Rx—The Patients' Fight for Medicinal Pot*. New York: Thunder's Mouth Press, 1998: 467.

⁶⁸⁴personal communication, Dr. Scott Morrow, San Mateo County Health Department, May 16, 2000.

Now that this historical review has reached the present, a major opportunity remains in the effort to gain a deeper understanding of past and current policies of FDA regarding psychedelic and medical marijuana research. Chapter 3 consists of a careful examination of Pilot Drug and its role within FDA, of the circumstances that led to its establishment and demise, of the internal FDA dynamics that enabled Pilot Drug to reverse several decades of suppression of psychedelic research, and of its legacy for psychedelic and medical marijuana research, and for the FDA itself.