

CHAPTER 1
THE EVOLUTION OF THE REGULATION OF THE MEDICAL USES
OF PSYCHEDELIC DRUGS AND MARIJUANA

Scholarly investigations into the medical properties of psychedelic drugs and marijuana began in the United States in the 19th century within a completely open regulatory environment. The FDA was not yet established.⁴ Neither physicians⁵ nor pharmacists⁶ were required to have licenses. Consumers as well as physicians could purchase whatever drugs they chose without prescriptions.⁷ Medicines did not need to identify their contents.⁸ Research protocols did not need to be given prior approval by any Federal agency.⁹ Patients did not need to sign “informed consent forms” outlining the risks of participating in the research protocol.¹⁰ Protocols did not need to be approved by local Institutional Review Boards (IRB).¹¹ No state had yet established its own review

⁴Pure Food and Drug Act of 1906. 59 P.L. 384; 59 Cong. Ch. 3915; 34 Stat. 768. June 30, 1906.

⁵In 1889, the Supreme Court upheld the right of States to require licenses for physicians, which were to be obtained from State Boards of Health. Dent v. West Virginia, 129 U.S. 114 (1889). Justice Field, delivering the opinion of the Court, stated, “The power of the State to provide for the general welfare of its people authorizes it to prescribe all such regulations as, in its judgment, will secure or tend to secure them against the consequences of ignorance and incapacity as well as of deception and fraud.”

⁶Around the turn of the century, almost all pharmacists were licensed by State Boards. Temin P. *Taking Your Medicine: Drug Regulation in the United States*. Cambridge: Harvard University Press, 1980: 22.

⁷The Harrison Narcotic Act of 1914 required prescriptions for narcotics, but no other drugs. Sec 2 (a) and (b), 63 P.L. 223; 63 Cong. Ch. 1; 38 Stat. 785. January 17, 1914. Prescriptions for certain non-narcotic drugs began to be required by FDA after the passage of the Federal Food, Drug, and Cosmetic Act of 1938. 75 P.L. 717; 75 Cong. Ch. 675; 52 Stat. 1040. June 25, 1938.

⁸Prior to the Pure Food and Drug Act of 1906, the only federal regulation over the content of drugs was US Customs Service examination of all imported drugs. Drugs were to be forfeited if the manufacturer’s name and place of preparation was not accurately identified and were to be denied entry if it was determined that the drugs were adulterated or deteriorated. Importations of Drugs and Medicines Act of 1848. 30 Cong. Ch. 70; 9 Stat. 237. June 26, 1848.

⁹Prior federal approval to conduct clinical research in humans with unapproved drugs was required by Sec. 103 (b) of the 1962 Kefauver-Harris Amendments to the 1938 Food, Drug, and Cosmetic Act. 87 P.L. 781; 76 Stat. 780. October 10, 1962.

¹⁰Federal Policy for the Protection of Human Subjects, 56 FR 28,003 (June 18, 1991) (codified by adopting agencies in various sections of the Code of Federal Regulations). Also, FDA regulations governing informed consent can be found at 21 CFR 50 (1998).

board for approval of psychedelic or marijuana research.¹² Researchers did not need federal permits from the Drug Enforcement Administration to possess, administer or transport any psychedelic drug or marijuana.¹³ There were no national standards for the protection of research subjects.¹⁴ There was no additional review committee of the National Institute of Mental Health that had to approve all federally funded research projects in humans with psychedelics¹⁵ or Public Health Service review committee that had to approve all medical marijuana research projects in patient populations.¹⁶ There were no international codes of ethics for human research.¹⁷ ¹⁸ There were no international treaties that criminalized the non-medical uses of marijuana¹⁹ and psychedelics,²⁰ ²¹ authorized

¹¹Rules concerning IRBs were first issued on February 8, 1966 by the Surgeon General of the United States Public Health Service (USPHS). The National Institutes of Health (NIH) Policies for the Protection of Human Subjects were codified at 45 CFR 46 (1974). FDA regulations governing institutional review boards can be found at 21 CFR 56 (1998).

¹²California is the only such state, with the California Research Advisory Panel empowered to approve all research with Schedule I and II drugs. Cal Health & Saf Code § 11480 (2000): Research as to marijuana and hallucinogenic drugs; Research Advisory Panel; Membership; Proceedings.

¹³Controlled Substances Act of 1970. 91 P.L. 513; 84 Stat. 1236. October 27, 1970.

¹⁴45 CFR 46.

¹⁵On 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. Federally funded studies administering psychedelics to human subjects would need to be reviewed by this committee.

¹⁶Announcement of the Department of Health and Human Services' Guidance On Procedures for the Provision of Marijuana for Medical Research, May 21, 1999. <http://www.mpp.org/hhsguide.html>

¹⁷The Nuremberg Code on Permissible Medical Experiments, from *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10. Vol. 2, Nuremberg, October 1946 - April 1949*. Washington, DC: U.S. Government Printing Office, 1949: 181-182.

¹⁸Declaration of Helsinki. Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, and as revised by the 29th World Medical Assembly, Tokyo, Japan, 1975.

¹⁹The Single Convention on Narcotic Drugs (US Treaty Series Vol. 520, US Treaties and other International Agreements. Vol. 18 Part 2, 1967, p. 1407-1431.), which concluded on March 30, 1961, and entered into force in the United States on June 24, 1967. The Single Convention on Narcotic Drugs was amended by the 1972 Protocol Amending the Single Convention on Narcotic Drugs, 1961.

http://www.incb.org/e/ind_conv.htm

²⁰The Convention on Psychotropic Substances (US Treaty Series. Vol. 1019, US Treaties and other International Agreements. Vol 32 Part 1, 1979-80: 543-571) was concluded in Vienna, Austria on February 21, 1971. This treaty was a further expansion of the international system of controls on drugs and supplemented the Single Convention on Narcotic Drugs. The Convention on Psychotropic Substances was

licenses for scientists conducting medical research with psychedelics²² and marijuana,²³ or required annual production quotas for psychedelic drugs or marijuana used in research and medicine.^{24 25} All of these would come later (see chart).

Scientists in the 19th century faced an empty regulatory space when considering the conduct of human clinical research with psychedelics, marijuana or any other drug or device that they could obtain or invent.²⁶ Researchers could move from inspiration to implementation all in the same morning. The only constraint on the conduct of medical research came from non-binding medical codes of ethics. In 1847, The American Medical Association (AMA) adopted “Principles of Medical Ethics,” which didn’t explicitly discuss medical research. It’s core principle was the statement, “In every consultation, the benefit to be derived by the patient is of first importance.”²⁷ The oldest code of medical ethics was the Hippocratic Oath, attributed to the ancient Greek physician Hippocrates. The Hippocratic Oath’s primary tenet, to which adherence was voluntary, was “I will prescribe regimen for the good of my patients according to my ability and my judgment and

not self-executing and needed to be enacted into U.S. law to take effect domestically. The Psychotropic Substances Act of 1978, 95 P.L. 633, 92 Stat. 3768. November 10, 1978 was written to “enable the United States to meet all of its obligations under the Convention.” The treaty itself entered into force with respect to the United States on July 15, 1980. http://www.incb.org/e/ind_conv.htm

²¹ The Single Convention on Narcotic Drugs and the Convention on Psychotropic Substances were further supplemented by the United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, December 20, 1988, ratified by the US in the International Narcotics Control Act of 1992 102 P.L. 583; 106 Stat. 4914. November 2, 1992. http://www.incb.org/e/ind_conv.htm

²² Article 8 of the Convention on Psychotropic Substances.

²³ Article 30 of the Single Convention on Narcotic Drugs.

²⁴ Articles 12, 19-21 of the Single Convention on Narcotic Drugs, Article 16 of the Convention on Psychotropic Substances. Quotas on production of Schedule I drugs are in Section 306 of the CSA (21 U.S.C. 826).

²⁵ For an overview of the international treaties, see Rexed B, Edmondson K, Khan I and Samsom R. *Guidelines for the Control of Narcotic and Psychotropic Substances—In the context of the international treaties*. Geneva: World Health Organization. 1984.

²⁶ “...no 19th century federal legislation dealt generally with the safety or effectiveness of food and drugs marketed throughout the United States.” Hutt P, Merrill, R. Historical Background—The Evolution of Federal Food and Drug Legislation. *Food and Drug Law: Cases and Materials-Second Edition, University Casebook Series*. Westbury, New York: Foundation Press, 1991: 8.

²⁷ Fishbein M. *A History of the American Medical Association, 1847-1947*. Philadelphia: Saunders, 1947, 35-40. The core elements of the code were initially proposed in 1803 by Thomas Percival, an English physician. About as close as the AMA’s code got to addressing medical research was the statement, “It is unprofessional to promise radical cures; to boast of cures and secret methods of treatment and remedies.”

DEVELOPMENT OF REGULATIONS GOVERNING MEDICAL RESEARCH WITH PSYCHEDELICS AND MARIJUANA IN THE U.S.								
CELLS IN BOLD REPRESENT U.S. LAWS, REGULATIONS, GUIDELINES THAT DIRECTLY INFLUENCE RESEARCH								
						REVIEW OF	PHS REVIEW	
		CREATION OF FDA	FDA/NIDA	CONTROL OVER	DEA	NIH-FUNDED	OF MEDICAL	INT. TREATIES
INFORMED	IRB	PRIOR IND	Advisory Comm.	NON-MEDICAL	LICENSING OF	PSYCHEDELIC	MARIJUANA	REG. OF RESEARCH
CONSENT	APPROVAL	APPROVAL	Guidelines	USE OF DRUGS	PHYSICIANS	PROTOCOLS	PROTOCOLS	PROD. QUOTAS
						Fed. Funded Only	Priv. funded	
Nuremburg, 1947		Pure Food & Drug Act of 1906	NIDA Technical Review of	Harrison Narcotic Act of 1914				Single Convention
	FIRST NIH				Controlled	FDA/NIMH	HHS	
1962 Amendments to 1938 Act	Intramural Review, 1953	June 1906	Hallucinogens	December 1914	Substances	Committee	Guidelines	On Narcotic
October 1962			July 1992		Act of 1970	Review, 1967	May 1999	Drugs
	DHEW Rules, February 1966	1938 Amends. to 1906 Act	FDA Drug Abuse Advisory Cmt	Marijuana Tax Act of 1937	October 1970			June 1967
Helsinki, 1964		June 1938	July 1992	August 1937		Controlled		Psychotropic
Revised,						Substances		Substances Act
Hong Kong, 1989	DHEW Rules			Drug Abuse		Act of 1970		November '78
	May 1974	1962 Amends. to 1938 Act		Control Amend. of 1965		Regulating		
Belmont, 1978		October 1962		July 1965		Treatment of		US Ratifies
HHS 45 CFR 46	HHS 45 CFR 46 Rev., March 1983					Narcotic Addicts		Convention on
Revised, March 1983				LSD Possession		October 1970		Psychotropic
				Restric. 1968				Substances
Common Rule	Common Rule			October 1968		NIDA Guidelines		July 1980
16 Fed. Agencies	June 1991					For Research		
June 1991	FDA Rules			Controlled		With Drugs Of		UN Convention
FDA Rules	June 1991			Substances		Abuse and Drug		Against Illicit
June 1991				Act of 1970		Abusers		Traffic in Narcotic
				October 1970		June 1997		Drugs and Psycho-
								Tropic Substances
National Bioethics						NIMH Policy		1988
Advisory Committee				Emergency Sch. of MDMA, 1985		Statement For		
June 1999				July 1985	21 USC 823 (b)	Research in		International
FDA 21 CFR 50	FDA 21 CFR 56	21 CFR 312			21 CFR 1301	Mentally-III		Conference on
	HHS 45 CFR 46			Controlled		Patients		Harmonization
				Substances		January 1999		Of Technical
				Analogue Act				Requirements for
				October 1986				Registration of
								Pharmaceuticals
								for Human Use
				21 USC (801)				1989
				21 CFR 1308.11				

never do harm to anyone. To please no one will I prescribe a deadly drug, nor give advice which may cause his death.”²⁸

In today’s regulatory context, researchers who have private, non-governmental funding to conduct psychedelic and medical marijuana research in patient populations need to budget a minimum of three to six months for the protocol design and approval process.²⁹ The likelihood of obtaining final approval is greater for psychedelic research than for medical marijuana research.³⁰ Researchers seeking federal funding for psychedelic and medical marijuana research in patient populations need to budget at least a year for the grant review process,³¹ with the likelihood of obtaining a grant for medical marijuana research greater than that for psychedelic research.³²

ERA OF OPEN ACCEPTANCE - 1874-1962

Psychedelic Research Begins

Psychedelic research can be considered to have begun in earnest in the United States around 1874. At that time, Benjamin Paul Blood self-published a 37-page pamphlet that described in detail the insights into consciousness and philosophy that he derived from his self-experiments with the inhalation of nitrous oxide gas.³³ Nitrous oxide had been discovered in 1772 by Joseph Priestley in England,³⁴ where over the following decades its anesthetic and inebriating qualities had attracted the most attention.³⁵ Though nitrous oxide was used in the United States for entertainment in carnival side shows and as an

²⁸Hippocrates lived from 460 BC - 377 BC. With surprising relevance to modern medical controversies, the Hippocratic Oath also proscribed abortion, and sex between doctor and patient.

²⁹For several decades, neither pharmaceutical companies nor major foundations have provided funding for psychedelic psychotherapy research.

³⁰Due to issues related to the different sources of supply for research-grade marijuana and psychedelics. This is discussed more fully in Chapter 2.

³¹The National Institutes of Health grant cycles take about a year from initial submission to dispersal of funds.

³²Due to issues related to differences in levels of public support for research into the medical properties of marijuana and psychedelics. This is discussed more fully in Chapter 2.

³³Blood B. *The Anesthetic Revelation and The Gist of Philosophy*. Amsterdam, N.Y. [no publ.]: 1874. 37 pages.

³⁴Priestley also discovered oxygen, nitrogen and ammonia. He was driven out of England in 1791 as a result of his revolutionary political views and subsequently emigrated to America.

³⁵Davy H. *Researches, Chemical and Philosophical; Chiefly Concerning Nitrous Oxide, or Dephlogisticated Nitrous Air, and its Respiration*. London: Printed for J. Johnson by Biggs and Cottle, Bristol, 1800.

anesthetic in dentistry from the 1840s onward,³⁶ Blood was the first person in the United States to publish a systematic discussion of the psychological and philosophical implications of the subjective effects of nitrous oxide.

In 1882, Harvard psychologist William James, after reading and being inspired by Benjamin Paul Blood's 1874 pamphlet, published his own paper about the subjective effects of nitrous oxide.³⁷ James discussed his self-experiments with nitrous oxide and reported that these experiences had assisted him to better understand Hegel's philosophy of the unification of opposites within a higher-order synthesis. James remarked:

The keynote of the experience is the tremendously exciting sense of an intense metaphysical illumination. Truth lies open to the view in depth beneath depth of almost blinding evidence. The mind sees all the logical relations of being with an apparent subtlety and instantaneity to which its normal consciousness offers no parallel; only as sobriety returns, the feeling of insight fades, and one is left staring vacantly at a few disjointed words and phrases, as one stares at a cadaverous-looking snowpeak from which the sunset glow has just fled, or at the black cinder left by an extinguished brand.³⁸

In 1887, clinical research into the peyote cactus began in the United States with the publication by Dr. J.R. Briggs of Dallas, Texas of an article reporting the results of his self-experimentation with peyote.³⁹ The peyote cactus, which had been used for at least two millennia in religious rituals by Native Americans in Mexico,⁴⁰ had come to the attention of Dr. Briggs as a result of its use by North American Indians.⁴¹ Dr. Briggs mailed 5 bushels of peyote to Parke-Davis Pharmaceutical company, Detroit, Michigan, which that same year mailed dried samples to Berlin pharmacologist Louis Lewin for analysis.

³⁶For more information about the history of Nitrous Oxide, see Shedlin M, Wallechinsky D, with Salyer S. (eds.) *Laughing Gas—Nitrous Oxide*. Berkeley: Ronin Press, 1992.

³⁷James W. Subjective Effects of Nitrous Oxide. *Mind* 7 (1882): 186-208.

³⁸*Ibid.*

³⁹ Briggs J. Mescale Buttons—Physiological Effects: A Mexican Fruit with Possible Medicinal Virtues. *Medical Register* 1 (April 7, 1887): 276-77.

⁴⁰Hofmann A, Schultes R. *Plants of the God*. Maidenhead, England: McGraw-Hill, 1979: 48.

⁴¹Stewart O. *Peyote Religion: A History*. Norman, Oklahoma: University of Oklahoma Press, 1987: 7. For a discussion of a Supreme Court case (*Employment Division of Oregon v. Smith*) involving Native American claims of a religious freedom exemption to laws criminalizing the use of peyote, see Smith, Huston and Snake, Reuben. *One Nation Under God—The Triumph of the Native American Church*. Santa Fe: Clear Light Publishers, 1996.

In 1888, Dr. Lewin published the first report of the chemistry of peyote.⁴² On July 23, 1897, mescaline was identified as the primary psychoactive component of peyote by Dr. Arthur Heffter, a full professor at Leipzig Institute, Germany. Dr. Heffter had conducted a self-experiment testing mescaline, which he had extracted from peyote, for psychoactive effects.⁴³ In 1897, the editor of the prominent Journal of the American Medical Association published a description of the subjective effects of peyote in a non-Native American. The report was written by A. Weir Mitchell,⁴⁴ a physician and author from Philadelphia who subsequently introduced William James to peyote.⁴⁵ James commented that the nausea he experienced after consuming a small amount of the peyote made him decide to “take the visions on trust.”⁴⁶

James continued to experiment with nitrous oxide, which did not make him nauseous. In his 1902 classic *Varieties of Religious Experience*, James discussed how his nitrous oxide experiences helped him generate hypotheses about the workings of consciousness itself. His comments hint at some of the reasons for the enduring nature of scholarly, scientific interest in psychedelic research. According to James:

Our normal waking consciousness, rational consciousness as we call it, is but one special type of consciousness, whilst all about it, parted from it by the flimsiest of screens, there lie potential forms of consciousness entirely different. We may go through life without suspecting their existence, but apply the requisite stimulus, and at a touch they are there in all their completeness, definite types of mentality which probably somewhere have their field of application and adaptation. No account of the universe in its totality can be final which leaves these other forms of consciousness quite disregarded. How to regard them is the question — for they are so discontinuous with ordinary consciousness. Yet they may determine attitudes though they cannot furnish formulas, and open a region though they fail to provide a map. At any rate, they forbid a premature closing of our accounts with reality.⁴⁷

⁴²Lewin L. Über Anhalonium lewinii. *Archiv für Experimentelle Pathologie und Pharmakologie* 24 (1888): 401-411.

⁴³Holmstedt B, Liljestrang G, eds. *Readings in Pharmacology*. New York: The Macmillan Company, 1963: 208-209.

⁴⁴Editor. Dr. S Weir Mitchell’s Experiments with the Mescal Button. *JAMA*28 (1897): 501-503, reporting on Mitchell S. The Effects of Anhalonium Lewinii (the Mescal Button). *British Med J* 2 (1896): 1625-1629.

⁴⁵Klüver H. *Mescal and Mechanisms of Hallucinations*. Chicago: University of Chicago Press, 1966: 15-17.

⁴⁶*Ibid.*, 17.

Nitrous oxide is still in medical use in 2000, as a dental anesthetic. It has been compared favorably to alternative anesthetic medications since it is not considered to impair higher cognitive tasks such as memory after the sedation wears off.⁴⁸

The Pure Food and Drugs Act of 1906

Support for the passage of some regulations over the food and drug supply had been building for several years prior to the passage of the 1906 Act. In 1906, the United States Congress passed the Pure Food and Drugs Act,⁴⁹ in large part as a result of public outrage about unsanitary conditions in the meatpacking industry generated by Upton Sinclair and other muckrakers⁵⁰ and concerns over fraudulent patent medicines exposed in a ten-part Colliers series by Samuel Hopkins Adams.⁵¹ This Act primarily focused regulatory attention on the advertising, labeling and purity of foods and drugs sold in interstate commerce. This was the first major Federal legislation that attempted to control food and drugs that were neither imported nor exported, but solely marketed within the United States. Enforcement authority was vested in the Department of Agriculture.

Medicines and foods that contained a specified list of “narcotic” drugs such as morphine, heroin, opium, cocaine and cannabis indica were specifically required to disclose on the label the amounts of such drugs that were present.⁵² No psychedelic drugs were included in this list. No restrictions were placed on maximum potencies, advertising, or age of consumer. Premarketing approval by FDA for any drug, even those narcotics whose presence had to be disclosed in foods and medicines, was not required. All these medications could be sold over the counter.

The primary enforcement mechanism created by the Act was the requirement that the labeling on the package of food or drugs not be “false or misleading in any particular.”⁵³ Manufacturers were subject to penalties if foods or drugs contained

⁴⁷James W. *Varieties of Religious Experience* New York: MacMillan Publishing, 1961 edition: 305.

⁴⁸Thompson J, Neave N, Moss M, Scholey A, Wesnes K, Girdler N. Cognitive properties of sedation agents: comparison of the effects of nitrous oxide and midazolam on memory and mood. *British Dentistry Journal* 187 (Nov 27, 1999) 10:557-62.

⁴⁹Pure Food and Drugs Act 59 P.L. 384; 59 Cong. Ch. 3915; 34 Stat. 768. June 30, 1906.

⁵⁰Sinclair U. *The Jungle*. New York: Doubleday and Co., 1906.

⁵¹FDA CDER Timeline: Chronology of Drug Regulation in the United States.

<http://www.fda.gov/cder/about/history/time1.htm>

⁵²A complete list of the psychoactive ingredients in medicines that had to be disclosed is found in Section 8, and includes “alcohol, morphine, opium, cocaine, heroin, alpha or beta eucane, chloroform, cannabis indica, chloral hydrate or acetanilide, or any derivative or preparation of any such substance contained therein.” None of these substances are psychedelic drugs. Foods were not required to disclose the presence of alcohol but otherwise the lists for medicines and foods were identical.

impurities or additives that were not listed on the label. By requiring full disclosure on the label, the Act helped provide consumers with accurate information about the contents of the food and drugs they purchased. However, dangerous ingredients in foods and drugs and ineffective ingredients in drugs could still be sold as long as their presence was disclosed on the label. While no false or misleading claims could be made about the contents themselves, the Supreme Court ruled in 1911 that the Act did not regulate medical claims on the label.⁵⁴ Furthermore, statements made by manufacturers that were not placed on the label, such as advertising, were not regulated.⁵⁵

The only check on claims of therapeutic efficacy that existed at this time was not regulatory in nature, but came from the American Medical Association's Council on Pharmacy and Chemistry. In 1905, the Council was established and instituted a policy requiring companies seeking to advertise in AMA and related journals to submit evidence supporting their claims to the Council. Only claims that were approved by the Council would be permitted to be included in advertisements.⁵⁶

The Harrison Narcotic Act of 1914

In 1909, the importation of opium for non-medical uses was criminalized,⁵⁷ but no further restrictions were placed on patent medicines containing opium, morphine, heroin, cannabis and other narcotic substances. In 1914, roughly at the midpoint between the 1906 Pure Food and Drugs Act and the enactment of Prohibition in 1920, the Harrison Narcotic Act established licensing, taxation and the control over the manufacture, sale and possession of opiates and cocaine.⁵⁸ Since the Harrison Act of 1914 involved taxation, enforcement authority was vested in the Treasury Department.⁵⁹

Medical uses of opiates and cocaine were not banned,⁶⁰ and research and

⁵³ Section 8, of Pure Food and Drugs Act.

⁵⁴ United States v. Johnson, 221 U.S. 488 (1911).

⁵⁵ The Sherley Amendment of 1912. 62 P.L. 301; 62 Cong. Ch. 352; 37 Stat. 416, August 23, 1912, did regulate false or misleading claims, but only if the manufacturer did not believe the claims, a factor difficult to prove.

⁵⁶ Fishbein M. *A History of the American Medical Association, 1847-1947*. Philadelphia: Saunders, 1947: 220-243. see also FDA CDER Timeline: Chronology of Drug Regulation in the United States. <http://www.fda.gov/cder/about/history/time1.htm>

⁵⁷ Opium, Restrictions on Importing Narcotic Drugs Import and Export Acts 60 P.L. 221; 60 Cong. Ch. 100; 35 Stat. 614, February 9, 1909. The International Opium Commission was the first international body that dealt with narcotic drugs, and met in Shanghai in 1909. The International Opium Convention was the first international drug control treaty, and was signed at the Hague in 1912.

⁵⁸ Harrison Narcotic Act of 1914. 63 P.L. 223; 63 Cong. Ch. 1; 38 Stat. 785. January 17, 1914.

⁵⁹ Sec 10, 63 P.L. 223; 63 Cong. Ch. 1; 38 Stat. 785.

treatment with these drugs could proceed without prior federal approval. However, for the first time for any drug, prescriptions from a licensed physician or dentist were required for patients to purchase medicines with quantities of opiates and cocaine above a specified limit.⁶¹ The physician, dentist⁶² and pharmacist⁶³ were all required to keep records for two years of all drugs dispensed or distributed.

Left unclear by the Act was whether the exception for the medical uses of opiates and cocaine meant that those drugs could be supplied to addicts by physicians as part of the treatment of addiction, either to prevent withdrawal through maintenance or to ease withdrawal through the provision of gradually decreasing doses. In 1919, the Supreme Court refused to review the convictions of several physicians and licensed druggists who had been arrested for providing large quantities of opiates to addicts without adequate medical care, in most cases primarily motivated by financial gain.⁶⁴ These convictions, sustained immediately prior to the establishment of Prohibition, were interpreted broadly as a warning that even the responsible provision of narcotics to treat narcotic addiction was illegal. Treasury agents aggressively prosecuted physicians who provided narcotics to patients, regardless of the impact of the prosecutions on the health status of the patients.⁶⁵ Although the Supreme Court subsequently clarified its position on this issue in 1925 when it ruled that the Harrison Narcotic Act did not prevent the medical use of opiates to treat addiction,⁶⁶ the medical profession remained intimidated and subsequently refrained from treating addicts with opiates.⁶⁷ According to John Kaplan, the ban was enforced by, “medical associations, state laws, threats of federal prosecution, and the whole range of governmental and non-governmental sanctions; nor was it disputed by the vast majority of medical practitioners, who regarded narcotic addicts as extremely difficult and unsatisfying patients.”⁶⁸

⁶⁰Sec. 2.

⁶¹Sec. 6.

⁶²Sec 2 (a). Physicians, dentists and veterinary surgeons were required to keep records for all prescriptions “except such as may be dispensed or distributed to a patient upon whom such physician, dentist and veterinary surgeon shall personally attend.”

⁶³ Sec 2 (b).

⁶⁴Trader v. United States, 260 F. 923 (3rd Cir. 1919). Oakshette v. United States, 260 F. 830 (5th Cir. 1919). Thompson v. United States, 258 F. 196 (8th Cir. 1919). Workin v. United States, 260 F. 137 (2nd Cir. 1919). Melanson v. United States, 256 F. 783 (5th Cir. 1919).

⁶⁵King R. Narcotic Drug Laws and Enforcement Policies. *Law Contemp Prob* 22 (Winter 1957): 122-123.

⁶⁶Linder vs. United States, 268 U.S. 5 (1925).

⁶⁷Lindesmith A. *The Addict and the Law*. Bloomington, Indiana University Press, 1965: 3-35.

⁶⁸Kaplan J. *The Hardest Drug: Heroin and Public Policy*. Chicago: University of Chicago Press, 1983: 63.

Halting the use of opiates to treat addiction is the first historical instance where the criminalization of the non-medical use of a class of drugs, in this case the opiates, gave enforcement authorities sufficient power to eliminate the medical use of the same drugs for certain indications, even though no legislation explicitly outlawed such medical uses. As will be described shortly, the medical use of marijuana also came to an end shortly after the passage of the Marijuana Tax Act of 1937, which was primarily aimed at non-medical users. The period from 1966-1990 of almost total suppression of psychedelic research followed a somewhat similar pattern in which psychedelic research, though not explicitly prohibited, was nevertheless increasingly proscribed after the non-medical use of LSD was criminalized.

Clinical research with mescaline and peyote was not affected by the Harrison Narcotic Act. At the University of Chicago, Dr. Kluver conducted research on the effect of mescaline on perception. In 1928, he published the first scientific monograph in English on the subject.⁶⁹ Research with mescaline also took place in Europe. In 1927, German physician Kurt Beringer published a description of his mescaline studies in research subjects.⁷⁰ One subject of his, who reportedly felt that the remarkable visual images he experienced should be captured in film, was subsequently hired by Walt Disney as the chief visualist for the Disney film, *Fantasia*.⁷¹

Marijuana Tax Act of 1937

Marijuana was first mentioned in an American medical text in 1843⁷² and was added to the United States Dispensary in 1854.⁷³ Dozens of research papers on various medical uses of marijuana were published in the medical literature during the late 19th and early 20th centuries.⁷⁴ The medical use of marijuana had not been affected by the 1906 Federal Pure Food and Drug Act or the Harrison Narcotic Act. Marijuana remained widely used in a variety of medical applications throughout the period of Prohibition. However, a growing sentiment against the non-medical use of marijuana was building at the state level and accelerated after the repeal of Prohibition in 1933.⁷⁵

⁶⁹Klüver H. *Mescal: The "Divine" Plant and its Psychological Effects*. London: Kegan Paul, Trench, Trubner and Co., 1928.

⁷⁰Beringer K. Der Meskalinrausch (The Mescaline Inebriation). *Monogra. Gesamtgeb. Neurology and Psychiatry* 49 (1927): 1-315.

⁷¹Stafford P. *Psychedelics Encyclopedia*. Berkeley: Ronin Publishing, 1992: 113. *Fantasia* was released in 1940. In an interview on 11/30/1999, Peter Stafford was unable to recall his source for this claim, which was not referenced in his book. However, he was confident the report was accurate.

⁷²Pereira J. *The Elements of Materia Medica and Therapeutics*. Philadelphia: Lea and Blanchard, 1843.

⁷³Abel E. *Marijuana: The First Twelve Thousand Years*. New York: Plenum, 1980.

⁷⁴Mikuriya T. *Marijuana: Medical Papers, 1839-1972*. Oakland: Medicomp, 1973.

In 1937, largely through what has been called “shrill propaganda by Federal authorities [especially Harry J. Anslinger, Commissioner of the Federal Bureau of Narcotics] in support of the Uniform Narcotic Drug Act,”⁷⁶ Congress passed the Marijuana Tax Act.⁷⁷ This Act was a revenue act with enforcement authority vested in the Treasury Department. The Act set fees of \$1 an ounce for specified industrial or medical uses⁷⁸ and \$100 an ounce for unspecified uses,⁷⁹ with tax evasion penalties for users who failed to pay the appropriate tax. The \$100 per ounce fee established for the non-medical, non-industrial use of marijuana effectively ended such uses. The \$1 tax on the medical use of marijuana was not sufficiently high to end the medical use of marijuana, which continued to be prescribed.

Ironically, prosecutions for failure to pay the tax for non-medical uses of marijuana as required by the Marijuana Tax Act were declared unconstitutional in 1969 by the United States Supreme Court in a marijuana possession case against Dr. Timothy Leary. The Court based its decision on the rationale that payment of the tax would violate the right against self-incrimination.^{80 81}

The 1938 Amendments to the Pure Food and Drug Act of 1906

As with the 1906 Act, efforts to enact a new law increasing the regulation of food and drugs preceded the passage of the 1938 Act by several years,⁸² with the impetus for

⁷⁵Bonnie R , Whitebread C. The Forbidden Fruit and the Tree of Knowledge: An Inquiry into the Legal History of American Marijuana Prohibition.” *Virg L Rev* 56 (1970) 971:1083-1149.

⁷⁶Bonnie R. *Marijuana Use and Criminal Sanctions*. Charlottesville, Virginia: The Michie Co., 1980: 1.

⁷⁷Marijuana Tax Act of 1937. 75 P.L. 238. 75 Cong. Ch. 553; 50 Stat. 551. August 2, 1937.

⁷⁸Sec 7 (a) (1).

⁷⁹Sec 7 (a) (2).

⁸⁰Leary v. United States, 395 U.S. 6 (1969). The Court stated, “At the time petitioner acquired marihuana [this was the preferred spelling at the time, but has been largely replaced by marijuana] he was confronted with a statute which on its face permitted him to acquire the drug legally, provided he paid the \$100 per ounce transfer tax and gave incriminating information, and simultaneously with a system of regulations which, according to the Government, prohibited him from acquiring marihuana under any conditions. We have found those regulations so out of keeping with the statute as to be ultra vires. Faced with these conflicting commands, we think petitioner would have been justified in giving precedence to the higher authority: the statute. 'Literal and full compliance' with all the statutory requirements" would have entailed a very substantial risk of self-incrimination.”

⁸¹Criminal sanctions against the non-medical possession of marijuana were placed on sound constitutional footing after Congress passed the Controlled Substances Act of 1970. 91 P.L. 513; 84 Stat. 1236. October 27, 1970.

⁸²FDA first proposed changes in the 1906 law in 1933, when a bill was introduced into the Senate but not passed.

final passage coming from a tragic incident that forced politicians to take action.⁸³ In 1937, 107 people, many of them children, died as a result of taking “Elixir Sulfanilamide,” a sore throat medicine that contained diethylene glycol, an untested ingredient used as a solvent with unexpected toxicity.⁸⁴ In 1938, in part as a result of public outrage against dangerous and impure medications, Congress passed the Federal Food, Drug, and Cosmetic Act of 1938, which substantially expanded and updated the 1906 Act.⁸⁵ Cosmetics⁸⁶ and devices⁸⁷ as well as drugs were subject to regulation. Manufacturing plants were subject to inspection.⁸⁸ The FDA could issue injunctions⁸⁹ as well as institute seizures and prosecutions.

The new Act required that, prior to obtaining approval for marketing, drug manufacturers submit to FDA a New Drug Application (NDA) containing adequate evidence demonstrating the safety of a drug for its intended uses.⁹⁰ The FDA was given a 60-day period within which to raise objections.⁹¹ If none were raised, the drug could be marketed. If objections were raised, no further requirements for a timely decision were placed on FDA. Prior FDA approval to conduct research in human subjects with new drugs, including marijuana and psychedelics, was not required, nor was pre-marketing proof of efficacy required.⁹²

Efficacy was still regulated primarily through the requirement that the labeling not be “false or misleading in any particular.” However, the 1938 Act eliminated the prior legal

⁸³Drayer J, Burns J. From Discovery to Market: The Development of Pharmaceuticals. *Burger’s Medicinal Chemistry and Drug Discovery. Fifth Edition, Vol. 1 Principles and Practices.* ed. Manfred Wolff. NY: Wiley and Sons, (1995): 254.

⁸⁴Young F. Commissioner of FDA, Remarks before Association of Food and Drug Officials, 92nd Annual Conference, Hartford, Ct. 6/23/1988. <http://www.fda.gov/bbs/topics/SPEECH/SPE00008.htm>.

⁸⁵Federal Food, Drug, and Cosmetic Act of 1938. 75 P.L. 717; 75 Cong. Ch. 675; 52 Stat. 1040. June 25, 1938.

⁸⁶Chap. 6, Sec. 601-604.

⁸⁷Sec. 201 {h} and Chap. 5, Sec 501-505.

⁸⁸Sec. 704. The development of Good Manufacturing Practices (GMP) began in 1941, after “nearly 300 deaths and injuries result from distribution of sulfathiazole tablets tainted with the sedative, phenobarbital.” FDA CDER Timeline: Chronology of Drug Regulation in the United States. <http://www.fda.gov/cder/about/history/time1.htm>

⁸⁹Sec. 302.

⁹⁰Sec. 505 (b) 1.

⁹¹Sec 505 (c).

⁹²Sec. 505 (i) “The Secretary shall promulgate regulations for exempting from the operation of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety of drugs.”

requirement that claims were to be considered false or misleading only if the manufacturer or marketer had an intent to defraud.⁹³

The 1938 Act also contained several important provisions changing FDA policy regarding the labeling requirement for drugs. The quantity of all active ingredients needed to be included on the label,⁹⁴ as well as explicit directions for the safe use of the product, with warnings about dangers.⁹⁵ For the first time, a psychedelic drug, peyote, came under regulation, with the requirement that any drug that contained any amount of a specified list of narcotic and hypnotic drugs (including opium, heroin, codeine, cocaine, marijuana, and peyote, and derivatives of all the drugs, which also brought mescaline under the regulations) had to be sold with a label that said, “Warning - May be Habit Forming.”⁹⁶ The fact that Congress decided to include peyote in this list suggests that either the use of peyote by members of the Native American Church or the medical research with mescaline had attracted the attention of FDA or some Congressional representatives. No other restrictions were placed on the sale of peyote or mescaline, and both could still be purchased by anyone without prescription.

The most important change to the labeling requirements was the option given to drug manufacturers to opt out of providing any information whatsoever on the label other than a general warning, the exact language of which would be determined by FDA, as long as the label was “not necessary for the protection of the public health.”⁹⁷ This provision was interpreted by FDA to mean that the full information required on the label would not be necessary if the manufacturer would agree that the drug would be made available to patients only by prescription from a physician. As a result of this opportunity for manufacturers to seek an exemption from the labeling requirements, two classes of non-narcotic drugs were created, over-the-counter drugs that anyone could purchase without a prescription, and prescription drugs available only with a prescription from a physician. The limits on consumer choice and self-medication that the current regulations enforce got their start in 1938, despite the claims of the drafters of the law that self-medication was not meant to be threatened by the new law.⁹⁸

The Gradual Prohibition of Marijuana’s Medical Use

Continued lobbying against the medical use of marijuana by Commissioner

⁹³Sec. 201 (n).

⁹⁴Sec. 502 (b) (2).

⁹⁵Sec. 502 (f).

⁹⁶Sec. 502 (d).

⁹⁷Sec. 502 (f) (2).

⁹⁸Temin P. The Origin of Compulsory Drug Prescriptions. *J Law Econ*(April 1979): 91-105. The dual system of over-the-counter and prescription drugs was formalized in the Durham-Humphrey Amendment of 1951, 82 P.L. 215; 82 Cong. Ch. 578; 65 Stat. 648. October 25, 1951.

Anslinger contributed to the gradual delegitimization of marijuana's medical uses. In 1941, marijuana was removed from the United States Pharmacopeia and National Formulary.⁹⁹ For the second time, the non-medical use of a drug was criminalized, which led in relatively short order to the suppression of its medical uses.

The national security concerns of World War II catalyzed an increase in government-funded research into the possible uses of an expanding number of psychedelic drugs and marijuana as non-lethal incapacitants, brainwashing and interrogation agents.¹⁰⁰
¹⁰¹ ¹⁰² In the United States, this research was conducted under the auspices of the Office of Strategic Services (OSS), the predecessor to the CIA.¹⁰³ While the removal of marijuana from the National Formulary in 1941 prevented medical physicians from prescribing marijuana, in 1942 the OSS initiated an active program of research into the potential use of marijuana as a truth serum. Commissioner Anslinger became a member of the OSS research committee.¹⁰⁴

In 1945, after a period of debate regarding the actual dangers of marijuana, the American Medical Association finally yielded to continuing pressure from Commissioner Anslinger¹⁰⁵ and published an editorial concurring in the view that marijuana was “a menace wherever it is purveyed.”¹⁰⁶ Clinical research with marijuana was still legally possible if prior permission was obtained from the Federal Bureau of Narcotics, but no non-military research actually took place. Thus, criminalization of a drug not only suppressed its medical use but further had the effect of squelching medical research.

The Discovery of LSD

LSD was first synthesized in 1938 by Dr. Albert Hofmann, a Swiss chemist working for Sandoz Pharmaceuticals, in the hope of developing a “circulatory and respiratory stimulant (an analeptic).”¹⁰⁷ After some initial animal testing that didn't seem

⁹⁹Grinspoon L and Bakalar J. *Marijuana: The Forbidden Medicine*. New Haven: Yale University Press, 1993: 8.

¹⁰⁰Lee M, Schlain B. *Acid Dreams- LSD, the CIA and the Sixties Rebellion*. New York: Grove Press, 1985.

¹⁰¹Marks J. *The Search for the Manchurian Candidate*. New York: Times Books, 1979.

¹⁰²Buckman J. Brainwashing, LSD, and CIA: Historical and Ethical Perspective. *Int J Soc Psychiat* 23 (Spring 1977) 1:8-19.

¹⁰³The CIA was created in 1947 and dramatically expanded military-related psychedelic research. National Security Act of 1947. 80 P.L. 253; 80 Cong. Ch. 343; 61 Stat. 495. July 26, 1947.

¹⁰⁴Lee, Schlain: 1.

¹⁰⁵Anslinger H. The Psychiatric Aspects of Marijuana Intoxication. *JAMA* 121 (1943): 212-213.

¹⁰⁶Editorial. Marijuana Problems. *JAMA* 127 (1945): 1129.

¹⁰⁷Hofmann A. *LSD- My Problem Child*. New York: McGraw-Hill, 1980: 12.

promising, no further work was conducted. On April 16, 1943, Dr. Hofmann resynthesized some LSD after having “ a peculiar presentiment- the feeling that this substance could possess properties other than those established in the first investigations...This was quite unusual.” While resynthesizing the LSD, Dr. Hofmann discovered the psychedelic properties of LSD as a result of an accidental exposure to a minute amount of LSD. His lab notes for that day report:

I was forced to interrupt my work in the laboratory in the middle of the afternoon and proceed home being affected by a remarkable restlessness, combined with a slight dizziness. At home I lay down and sank into a not unpleasant intoxicated-like condition, characterized by an extremely stimulated imagination. In a dreamlike state, with eyes closed (I found the daylight to be unpleasantly glaring), I perceived an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colors. After some two hours this condition faded away.¹⁰⁸

Dr. Hofmann decided to conduct a planned experiment to determine if LSD had somehow been the cause of his unusual experiences. Three days later, he cautiously self-administered 250 micrograms, an amount he thought would make a very small dose but which is now considered to generate a full psychedelic experience. As a result of his self-experiment, Dr Hofmann confirmed the astonishing psychological power of extremely small amounts of LSD. He reported:

I had to struggle to speak intelligibly. I asked my laboratory assistant, who was informed of the self-experiment, to escort me home. We went by bicycle, no automobile being available because of wartime restrictions... In spite of my delirious, bewildered condition, I had brief periods of clear and effective thinking... Every exertion of my will, every attempt to put an end to the disintegration of my ego, seemed to be wasted effort. I was seized by the dreadful fear of going insane. I was taken to another world, another place, another time. My body seemed to be without sensation, lifeless, strange. Was I dying? ...Slowly I came back from a weird, unfamiliar world to reassuring everyday reality...Now, little by little, I could begin to enjoy the unprecedented colors and plays of shapes that persisted behind my closed eyes...Exhausted, I then slept, to awake the next morning refreshed with a clear head...Breakfast tasted delicious and gave me extraordinary pleasure. When I later walked out into the garden, in which the sun shone now after a spring rain, everything glistened and sparkled in a

¹⁰⁸Ibid., 15.

fresh light. The world was as if newly created. All my senses vibrated in a condition of highest sensitivity, which persisted for the entire day...

I could remember the experience of LSD inebriation in every detail. This could only mean that the conscious recording function was not interrupted, even in the climax of the LSD experience, despite the profound breakdown of the normal world view...

Since my self-experiment had revealed LSD in its terrifying, demonic aspect, the last thing I could have expected was that this substance could ever find application as anything approaching a pleasure drug. I failed, moreover, to recognize the meaningful connection between LSD inebriation and spontaneous visionary experience until much later, after further experiments, which were carried out with far lower doses and under different conditions.¹⁰⁹

Dr. Hofmann and his associates at Sandoz theorized that LSD might have a dual role in medicine, in helping researchers to understand and treat mental illness, and in training psychiatrists, who would be able to experience a “model psychosis” so as to gain insight into the inner world of their patients. The first scientific paper on the effects of LSD was published in 1947. It reported on the administration of LSD by Sandoz researchers to 16 healthy normals and 6 schizophrenics.¹¹⁰

1947- Nuremberg Code

At the end of World War II, Allied authorities liberated the Nazi concentration camps and learned that Nazi doctors at Dachau and elsewhere had conducted horrific medical experiments on prisoners. Many of these studies were explicitly designed to result in the death of the experimental subjects.¹¹¹ In some mind-control studies at Dachau, mescaline was administered.¹¹² The horrors of the Nazi experiments were exposed to the world during the Nuremberg trials and in subsequent books.¹¹³ The Nuremberg judges had dual responsibilities, to punish the perpetrators of the inhumane medical experiments and to do what was in their power to prevent the recurrence of similar atrocities. In 1947, the Nuremberg Judges proposed the first formal code of ethics for human research,

¹⁰⁹Ibid., 16-20.

¹¹⁰Stoll W. Lysergsäure-diäthyl-amid, ein Phantastikum aus der Mutterkorngruppe. [LSD, a hallucinatory agent from the ergot group] *Schweiz. Arch. Neut.* 60 (1947).

¹¹¹Lifton R. *The Nazi Doctors: Medical Killing and the Psychology of Genocide*. New York: Basic Books, 1986.

¹¹²Lee, Schlain: 6.

¹¹³Annas G, Grodin M, eds. *The Nazi Doctors and the Nuremberg Code: Human Rights in Human Experimentation*. Oxford: Oxford University Press, 1992.

containing 10 basic principles.¹¹⁴ Among the most important principles were the requirements that subjects give voluntary consent to participate in any study, that there be a balance between the risks to the subjects with the knowledge to be gained for the benefit of society, that all unnecessary physical and mental suffering and injury be avoided, and that the subject remain free to withdraw from the study at any point without penalty. The Nuremberg Code had informal moral authority, but was not enacted into US law or regulation.

The Expansion of LSD Research

After its initial in-house research, Sandoz began to distribute LSD free to researchers around the world in exchange for research data, in the hope that a useful and lucrative application for LSD would be discovered.¹¹⁵ LSD first appeared in the United States in 1949, when Dr. Robert Hyde, Associate Director of the Harvard-affiliated Boston Psychopathic Hospital (now Massachusetts Mental Health Center, still affiliated with Harvard) conducted a self-experiment with the assistance of Dr. Max Rinkel.¹¹⁶ Later in 1949, Dr. Rinkel, also at Boston Psychopathic, was the first American to administer LSD to a research subject.¹¹⁷ In 1950, the first paper based on research conducted in the United States was published by Drs. Busch and Johnson, who tested LSD on neurotic patients who had not been greatly helped by alternative treatments. They reported “a reliving of repressed traumatic episodes of childhood,” and concluded, “on the basis of the preliminary investigation, L.S.D. 25 may offer a means for more readily gaining access to the chronically withdrawn patients. It may also serve as a new tool for shortening psychotherapy. We hope further investigation justifies our present impression.”¹¹⁸

The discovery of LSD, of which extraordinarily small amounts had powerful psychological effects, attracted the attention of the Central Intelligence Agency (CIA), which began in 1951 to explore its use.¹¹⁹ CIA research was conducted by CIA employees and through grants to outside researchers. Some of this early CIA-funded LSD research took place at Harvard, under the direction of Dr. Robert Hyde.¹²⁰ In San

¹¹⁴The Nuremberg Code on Permissible Medical Experiments, from *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10. Vo. 2, Nuremberg, October 1946 - April 1949*. (Washington, DC: U.S. Government Printing Office, 1949): 181-182.

¹¹⁵Lee, Schlain: 26.

¹¹⁶Stafford: 39.

¹¹⁷Rinkel M, DeShon H, Hyde R, Solomon H. Experimental schizophrenia-like symptoms. *Amer J Psychiat* 108 (1952): 4572.

¹¹⁸Busch A, Johnson W. LSD 25 as an Aid in Psychotherapy (Preliminary Report of a New Drug). *Dis Nerv Syst* 11 (1950): 243.

¹¹⁹Lee, Schlain: 13.

Francisco, a series of experiments were carried out for over a decade using unwitting volunteers. In some cases, subjects were lured by prostitutes to an experimental setting disguised as a brothel, then dosed with LSD and observed through one-way mirrors.¹²¹ These experiments and others like them by security agencies in other countries had occasionally devastating results. Lawsuits are still ongoing against the US, British and Canadian governments, filed by subjects seeking damages for their participation in some of the more irresponsible and unethical government-conducted LSD testing programs.¹²²
123 124

Beginning in 1953, the National Institute on Mental Health (NIMH) also began funding LSD research,¹²⁵ while other projects were funded by foundations, universities, private donors and, rarely, pharmaceutical companies. In 1953, Sandoz began a collaborative relationship with FDA, which distributed LSD on behalf of Sandoz to US-based federally-funded researchers, and to the CIA research projects.¹²⁶ The primary evaluation of protocols was conducted by NIMH in the context of its funding decisions. FDA provision of LSD was essentially automatic, with no protocol review conducted or requirement to submit clinical data to FDA for evaluation. Sandoz also distributed LSD

¹²⁰Lee, Schlain: 20.

¹²¹Lee, Schlain: 32.

¹²²Dyer C. Patients given LSD may be able to claim compensation. *BMJ* 311 (Nov 4, 1995) 7014: 1185-6.

¹²³Kelso P. Patients sue over LSD treatment side effects. *Guardian* (UK), page 2, Wednesday November 17, 1999.

¹²⁴Tyler T. Prisoners Used for Frightening Tests, New Papers Show. *Toronto Star*, Dec. 18, 1999. According to the article, "Ottawa approved using inmates to test everything from steroid enemas to links between height and crime while Canada's prison system operated as a research lab, federal documents show. The documents are contained in long-buried government files uncovered in the wake of a \$5 million lawsuit filed by Dorothy Proctor, one of 23 inmates involved in LSD experiments at Kingston's Prison for Women from 1960-63...The use of LSD and shock therapy in the Canadian prison system coincided with CIA-funded "brainwashing" experiments performed in Montreal at McGill University's Allan Memorial Institute between 1957 and 1961...In the McGill experiments, which were conducted by Dr. Ewen Cameron and also funded in part by the Canadian government, up to 130 people were given electroshock, high doses of LSD and subjected to taped messages." see also Blanchfield M and Bronskill J. Corrections Canada Assailed in Suit over LSD Experiment. March 3, 2000. *National Post* (Canada) <http://www.nationalpost.com> The article reports "The government used 'evasive' tactics to stonewall a former inmate's lawsuit over a prison LSD experiment, says a scathing court ruling that orders the head of Corrections Canada to testify in the case."

¹²⁵Szara S. Are Hallucinogens Psychoheuristic? *Hallucinogens: An Update*. NIDA Monograph Series # 146. Washington, DC, NIH Publication #94-3872, 1994: 33-51.

¹²⁶Lee, Schlain: 26.

directly to non-government funded researchers.¹²⁷

Dr. Albert Kurland, who eventually assembled and directed the largest and most productive group of psychedelic researchers in United States history, began to conduct LSD research in 1953 within a public hospital setting,¹²⁸ According to Dr. Kurland, it was relatively easy to obtain permission to conduct human research with psychedelics. He only needed to obtain permission for his research from the Hospital Administrator, and the subjects needed to sign a paper indicating they gave their consent to participate in the study.¹²⁹

In 1954 in Los Angeles, Dr. Oscar Janiger, a psychiatrist/researcher in private practice, began administering LSD to relatively healthy normals as well as artists in a naturalistic context designed to discover the commonalities of the LSD experience, Dr. Janiger's study was without government funding, with subjects including Cary Grant, Jack Nicholson, Anais Nin, Esther Williams, and other notables.¹³⁰ ¹³¹ Dr. Sidney Cohen, UCLA and LA Veterans Administration, studied LSD in healthy normals ¹³² as well as in more therapeutic contexts.¹³³

By the middle of the 1950s, LSD research was taking place in the United States, Switzerland, Germany, Italy, France, Czechoslovakia, Canada and several Scandinavian countries.

Early NIH Use of Peer Review

In 1953, the first federal requirement for committee review of research protocols was established, though this applied only to intramural research conducted at the new NIH Clinical Center and was not widely adopted.¹³⁴

¹²⁷personal communication, Myron Stolaroff, January 5, 2000.

¹²⁸Cholden L, Kurland A, Savage C. Clinical Reactions and Tolerance to LSD in Chronic Schizophrenics. *J Nerv Ment Dis* 122 (1955) 3:211-221.

¹²⁹personal communication, Dr. Albert Kurland, October 19, 1999.

¹³⁰Janiger O. The use of hallucinogenic agents in psychiatry. *California Clinician* 56 (1960): 222-224, 251-259. Janiger O, di Rios M. LSD and Creativity. *J Psyched Drug* 21 (1989):129-134.

¹³¹A long-term follow-up to Dr. Janiger's LSD research, conducted in part by this author, found that his subjects confirmed the relative safety and lack of long-term negative side effects from participating in LSD research, though whether a representative sample of subjects was located cannot be considered certain. Doblin R, Beck J, Obata K, Alioto M. Dr. Oscar Janiger's Pioneering LSD Research: A Forty Year Follow-up. *BullMAPS* 9 (Spring 1999) 1:7-23.

¹³²Cohen S, Fichman L, Eisner B. Subjective reports of lysergic acid experiences in a context of psychological test performance. *Am J Psychiat* 115 (1958): 30.

¹³³Eisner B, Cohen S. Psychotherapy with lysergic acid diethylamide. *J.Nerv Ment.Dis*127 (1958):528. Patients in this study suffered from different disorders including depressive states and borderline schizophrenia.

Mescaline, Psilocybin and Ayahuasca

The growing enthusiasm for the potential of LSD was matched by an increased interest in mescaline. In 1952, Dr. Humphry Osmond, a British psychiatrist, and his Canadian collaborator, Dr. John Smythies, published a scientific article about the relationship between mescaline, psychosis and schizophrenia.¹³⁵ Studies at the Manhattan State Hospital were conducted throughout the 1950s by Dr. Herman Denbar, who investigated the use of mescaline in a total of 350 psychiatric inpatients, mostly schizophrenics.¹³⁶ Several researchers sought to compare mescaline to LSD, which were reported to have very similar subjective effects.^{137 138 139}

In 1954, Dr. Osmond introduced Aldous Huxley to mescaline, who subsequently wrote a provocative and widely discussed account of his experience, *The Doors of Perception*¹⁴⁰ After the publication of *The Doors of Perception*, mescaline in particular and the psychedelic experience in general attracted substantial attention in non-medical circles. A counter-reaction to its use began to develop among some traditional religious academics who were uncomfortable with reports of drug-induced mystical experiences.¹⁴¹

¹³⁴Federal Regulation of Human Experimentation, 1975. Subcommittee on Health of the Committee of Labor and Public Welfare, United States Senate: U.S. Government Printing Office. N0 45-273-0, 1975.

¹³⁵Osmond H, Smythies J. Schizophrenia: A New Approach. *J Ment Sci*98 (1952): 309-315.

¹³⁶Denbar H, Merlis S. Therapeutic Aspects of the Mescaline-Chlorpromazine Combination. *J Nerv Ment Dis*122 (1955): 463-469. Denbar H. Mescaline and Lysergic Acid Diethylamide: Therapeutic Implications of the Drug-Induced State. *Dis Nerv Syst* 30 (1969 Feb) 2:Suppl: 23-7.

¹³⁷Koelle G. The Pharmacology of Mescaline and D-Lysergic Acid Diethylamide (LSD). *New Engl J Med* 258 (1958) 1:25-32.

¹³⁸Isbell H. Comparison of the Reactions Induced by Psilocybin and LSD 25 in Man. *Psychopharmacologia* 1 (1959): 29-38.

¹³⁹Wolbach A, Miner E, Isbell H. Comparison of Psilocin with Psilocybin, Mescaline and LSD 25. *Psychopharmacologia* 3 (1962): 219-223.

¹⁴⁰Huxley A. *The Doors of Perception*. New York: Harper, 1954. Huxley described the initial part of his experience as follows: "I took my pill at eleven. An hour and a half later, I was sitting in my study, looking intently at a small glass vase. The vase contained only three flowers—a full-blown Belle of Portugal rose, shell pink with a hint at every petal's base of a hotter, flammier hue; a large magenta and cream-colored carnation; and, pale purple at the end of its broken stalk, the bold heraldic blossom of an iris. Fortuitous and provisional, the little nosegay broke all the rules of traditional good taste. At breakfast that morning, I had been struck by the lively dissonance of its colors. But that was no longer the point. I was not looking now at an unusual flower arrangement. I was seeing what Adam had seen on the morning of his creation—the miracle, moment by moment, of naked existence."

¹⁴¹Zaehner RC. *Mysticism Sacred and Profane: an inquiry into some varieties of praeter-natural experience*. Oxford: Clarendon Press, 1957.

In 1955, Gordon Wasson, a New York banker with an intense fascination with mushrooms, discovered the continued existence of a long-hidden religious tradition involving the use of psychoactive mushrooms, practiced deep in the Mexican mountains by a medicine woman named Maria Sabina and others.¹⁴² Wasson sent samples of these mushrooms for analysis to Dr. Albert Hofmann, who published an article in 1958 reporting on his successful effort to synthesize and identify psilocybin as the principal active ingredient.¹⁴³ ¹⁴⁴ Wasson revealed his discovery in a main feature in *Life*¹⁴⁵ a venue provided by the publishers Henry and Clare Boothe Luce, both of whom had tried LSD with self-reported favorable results.¹⁴⁶

In the mid-1950s, a psychoactive tea from the Amazon called ayahuasca, or yage, had come to the attention of Allen Ginsberg, William Burroughs, and other representatives of the “Beatniks” such as Jack Kerouac and Neal Cassady. In 1956, Burroughs and Ginsberg wrote about their experiences with yage, drawing attention to the psychedelics from yet another direction.¹⁴⁷

World Health Organization Study Group

In 1958, the World Health Organization (WHO) published the findings of an international group of experts that it had convened to review the data from psychedelic studies conducted at research centers around the world.¹⁴⁸ The report was enthusiastic about the continuation of psychedelic research and rejected the use of the term “psychotomimetic” as an adequate description of the nature of the psychedelic experience. This report marks the last time that the WHO reviewed the field of psychedelic research, even though WHO has published an additional 738 publications in its Technical Report series since the 1958 report.¹⁴⁹

¹⁴²Wasson G, Wasson V. *Mushrooms, Russia and History*. New York: Pantheon Press, 1957.

¹⁴³Hofmann A, Heim R, Brack A, Kobel H. Psilocybin, ein psychotroper Wirkstoff aus dem mexikanischen Rauschpilz *Psilocybe mexicana* Heim. [Psilocybin, a psychotropic principle from the Mexican hallucinogenic fungus *Psilocybe mexicana* Heim]. *Experientia* 14 (1958): 107.

¹⁴⁴In 1962, Albert Hofmann and Gordon Wasson brought some synthesized psilocybin back to Mexico to Maria Sabina, who tried the pills containing psilocybin isolated in the laboratory and pronounced that the spirit of the mushroom was indeed in the pill. Hofmann A. Ride Through the Sierra Mazateca in Search of the Magic Plant “Ska Maria Pastora.” in *The Sacred Mushroom Seeker—Essays for R. Gordon Wasson*, ed. Thomas Riedlinger. Portland, Oregon: Discorideds Press, 1990, 115-127.

¹⁴⁵Wasson G. Seeking the Magic Mushroom. *Life* 42 (May 13, 1958): 19.

¹⁴⁶Lee, Schlain: 73.

¹⁴⁷Burroughs W, Ginsberg A. *The Yage Letters*. San Francisco: City Lights, 1956.

¹⁴⁸*Ataractic [tranquilizers] and Hallucinogenic Drugs in Psychiatry: Report of A Study Group*. Geneva: World Health Organization Technical Report Series, 1958 #152.

On the Cusp of Trouble

By the end of the 1950s, over 500 papers on LSD had been published.¹⁵⁰ In 1959, the first international conference on LSD therapy was convened, funded by the Josiah Macy Jr. Foundation, which had received funds from the CIA. The conference was chaired by Dr. Hyde, who had also received funds from the CIA.¹⁵¹ In 1960, Dr. Sydney Cohen reported on the results of his survey of forty-four psychedelic researchers whom he had contacted in an effort to ascertain the risk to subjects from participating in psychedelic research. The researchers reported the number of adverse effects in about 5000 patients who had taken LSD or mescaline more than a total of 25,000 times. The remarkably small number of adverse effects, which compared favorably to patients left untreated or treated with conventional medications, prompted Dr. Cohen to conclude, “considering the enormous scope of the psychic responses it induces, LSD is an astonishingly safe drug.”¹⁵² At this point in the history of psychedelic research, there seemed to be little basis from which to predict the turmoil that was soon to arrive.

Harvard Psychedelic Research

Beginning in 1960, Dr. Timothy Leary, lecturer in psychology, and Dr. Richard Alpert, assistant professor of psychology and education, along with a growing number of graduate students in Harvard’s Center for Research in Personality, began a series of experiments with psychedelic drugs. Psilocybin for research purposes was provided free to Dr. Leary by Sandoz. From the time these studies began, they generated an increasing amount of attention, controversy and backlash, and marked the concluding phase of the era of open acceptance of psychedelic research in the United States.

Dr. Leary and associates began by trying to characterize the subjective effects of psilocybin in a variety of naturalistic environments.¹⁵³ This study enrolled at least 175 subjects, the largest number of experimental subjects of all the Harvard studies. No regulations prohibited Drs. Leary or Alpert, who were not medical doctors, from

¹⁴⁹ Maristela G Monteiro, MD Ph.D., an official within the WHO Programme on Substance Abuse, has taken an interest in the use of psychedelics to treat substance abuse. She reports that research needs to be occurring in at least three different countries before the WHO could consider convening another study group. Personal Communication April 1996. See also Monteiro M. The Work of the WHO Program on Substance Abuse and Psychedelic Drugs. *Bull MAPS* 6 (1996) 3:2-5.

¹⁵⁰ Sandoz Pharmaceuticals Bibliography on Psychotomimetics 1943-1966. *Annotated Bibliography on Delysid (LSD 25) (d-lysergic acid diethylamide)*. Basel: Sandoz, 1966.

¹⁵¹ Stevens J. *Storming Heaven, LSD and the American Dream*. New York: Atlantic Monthly Press, 1987.

¹⁵² Cohen S. Lysergic acid diethylamide: side effects and complications. *J.Nerv Ment.Dis* 130 (1960):30-40.

¹⁵³ Leary T, Litwin G, Metzner R. Reactions to psilocybin in a supportive environment. *J Nerv Ment Dis* 137 (1963): 561-573.

administering psychedelic drugs to human subjects. Actual administration of the drugs did not even need to take place under medical supervision. The major guidelines that Dr. Leary established to govern the administration of psilocybin in naturalistic environments were that no subjects were to be given the drug alone; at least half the subjects in any experiment were to be “experienced” with the drug; a “warm, permissive naturally human setting” was provided, preparatory non-drug acquaintance meetings were provided to all subjects new to the drug or the group; and post-session follow-up discussions or meetings were to take place.¹⁵⁴

Over time, Dr. Leary expanded the research program to include an effort to catalyze remarkable and rapid behavior change in prisoners approaching parole, hypothesizing that the provision of positive psilocybin experiences could help reduce the recidivism rate.¹⁵⁵ Dr. Leary was also the academic advisor to Ph.D. candidate Dr. Walter Pahnke, a medical doctor and minister who conducted a double-blind placebo-controlled study of the potential of psilocybin to generate powerful mystical experiences in divinity students taking psilocybin in religious contexts.¹⁵⁶

In mid-1961, Dr. Leary began self-administering LSD, which he obtained from Michael Hollingshead, who had purchased it from Sandoz.¹⁵⁷ Intrigued by the effects of LSD, Dr. Leary subsequently began administering it to others, though he conducted formal research only with psilocybin. The advantages of psilocybin were described by Leary and associates as follows:

We have used several different substances (LSD, mescaline, psilocybin) and continue to be interested in the potential of all of these. In the course of our investigations, however, we have concentrated on the use of psilocybin because of certain advantages. Specifically, these advantages are (1), the duration of the major effect of the drug is short (about five hours), (2), there are minimal somatic side effects and (3) there are few cultural preconceptions regarding its effect...We have come to believe that psilocybin has the potential to facilitate for an individual the

¹⁵⁴Leary T. Newsletter #1, Research Program on Consciousness-Altering Substances, February 1962: 13.

¹⁵⁵Leary T, Metzner R, Presnell M, Weil G, Schwitzgebel R, Kinne S. A new behavior change pattern using psilocybin. *Psychother: Theor, Res Prac* 2 (1965) 2:61-72.

¹⁵⁶Pahnke W. *Drugs and Mysticism: An Analysis of the Relationship between Psychedelic Drugs and the Mystical Consciousness*. Unpublished doctoral thesis in the History and Philosophy of Religion submitted to Harvard University, 1963. See also Pahnke W. LSD and Religious Experience. in Debold R, Leaf R (eds.): *LSD, Man and Society*. Middletown, Conn.: Wesleyan University Press, 1967: 60-84. Also, Pahnke W. The Psychedelic Mystical Experience in the Human Encounter with Death. *Harv Theol Rev* 62 (1969): 1-21.

¹⁵⁷Stevens: 168.

experience of major insights and problem solutions of an intellectual-emotional nature.¹⁵⁸

As the number of people who had been given psilocybin grew larger, interest in the psychedelic research project spread among faculty and students at Harvard and at other institutions in the Boston area. A large planning meeting was held on October 8, 1961 attended by Professor Robert White, Chairman of the Department of Social Relations at Harvard, other members of the Harvard community, and representatives from a variety of institutions.

Not all participants in the October 8, 1961 meeting were convinced that psilocybin experiences were benefiting either the experimental subjects or the members of the research team. The most pointed criticism of the psilocybin experiments came from Dr. David McClelland, Director of Harvard's Center for Research in Personality. In a critique that now seems prescient, Dr. McClelland worried about the members of the research team, who were consuming rather large and frequent doses of psilocybin. He commented in a paper he prepared for the meeting:

Psilocybin appears to have promise, particularly in that it shakes up rapidly or disorganizes maladaptive habitual modes of thought (as in psychopaths) and results in insights into one's own behavior. The two chief problems an "outsider" sees are: 1. How to prevent it from disrupting adaptive modes of thought, perhaps especially among those who administer it, since they take it too, and 2. How to prevent the absorption in one's own thought processes from creating social withdrawal, insensitivity, impulsivity, and an unrealistic sense of omniscience.¹⁵⁹

According to Dr. Leary, "The consensus of this meeting was that this research was very exciting and should definitely be continued, but that a more formal administration was called for."¹⁶⁰ Among the changes were the creation of a small advisory board to review new research projects, and the addition of some medical safeguards. Dr. Leary arranged for basic medical screening of subjects to take place under the auspices of the Harvard University Health Services, with screening required prior to the participation of any subject in a research project. No undergraduates were allowed to participate in research studies and all subjects were supposed to be over 21 years of age.¹⁶¹ In case of emergency, University

¹⁵⁸Newsletter #1, Research Program on Consciousness-Altering Substances, February 1962: 1.

¹⁵⁹McClelland D. Some Social Reactions to the Psilocybin Research Project. Unpublished paper prepared for the October 8, 1961 meeting: 3.

¹⁶⁰Leary T. Letter to Dr. Carl Henze, Sandoz Laboratory, Medical Department, Hanover, New Jersey. November 14, 1961

Health Service doctors who were on 24-hour call were instructed to administer the major anti-psychotic tranquilizer, thiorazine, to “quiet the reaction.”¹⁶²

Qualifications for the leaders of experimental sessions at which psilocybin was administered were formalized. A nucleus group composed of three faculty, Drs. Leary, Alpert and Kahn, and five graduate students were all considered suitably trained to serve as group leaders. New research assistants were limited to those who were able to “show a strong interest in the program, complete the physical screening procedure, and participate in at least two psilocybin sessions with member(s) of the present group in one of which they serve as administrator. The results of these sessions are to be evaluated by the nucleus group. A decision will be reached on the basis of whether the group feels confidence in the individual’s ability to carry out a session.”¹⁶³

On November 14, 1961, Dr Leary sent a letter to Sandoz outlining the new administrative procedures and requesting an additional shipment of 2000 tablets of psilocybin.¹⁶⁴

On January 11, 1962, Drs. Leary and Alpert met informally with Mr. John Harvey, Deputy Commissioner of the FDA, and Dr. William Kessenich, also of the FDA. In a January 26, 1962 letter to Mr. Harvey, Dr. Leary summarized the content of the discussion by stating that “on the medical -- non-medical status of research drugs. It is our understanding that the Food and Drug Administration takes no position in this regard and there is no objection to usage by responsible, recognized non-medical scientists working in established institutional settings. The priority of state laws in this connection was recognized.”¹⁶⁵

In a January 1962 report to the Harvard community intended to inform and quell rumors, the research team reported that, “A recent rumor suggested that the punch at a University function had been “spiked” with hallucinogens by a student who obtained the material from us. In fact, our materials are carefully safeguarded and are signed out only to the members of our staff (who sign a requisition for all material) for specified research purposes. We were unable to ascertain the source of this rumor.”¹⁶⁶

On Good Friday, April 1962, Leary advisee Dr. Walter Pahnke conducted the

¹⁶¹Newsletter #1, Research Program on Consciousness-Altering Substances, February 1962: 12-13.

¹⁶²When a subject experiences a difficult reaction, most psychedelic researchers prefer to talk or offer non-verbal support to the subject until their mood changes and/or the effects of the drug wear off to a sufficient degree.

¹⁶³Newsletter #1, Research Program on Consciousness-Altering Substances, February 1962: 14.

¹⁶⁴Leary T. Letter to Dr. Carl Henze. November 14, 1961.

¹⁶⁵Leary, T. Letter to Mr. John Harvey, Deputy Commissioner, FDA. January 26, 1962. Reprinted in Newsletter #1, Research Program on Consciousness-Altering Substances, February 1962, 9-10. This author has not been able to locate any records of a reply from Dr. Harvey to Dr. Leary.

¹⁶⁶Newsletter #1, Research Program on Consciousness-Altering Substances, February 1962: 9.

classic “Good Friday” experiment at Marsh Chapel, at Boston University. Rev. Howard Thurman, Dr. Martin Luther King’s mentor, officiated during a Good Friday service at which twenty Andover Newton Theological Seminary students were randomly administered a pill containing either a strong dose of 20 milligrams of psilocybin or an active placebo of nicotinic acid. The experiment was designed as a randomized, double-blind matched control group study, with ten subjects in the psilocybin group and ten in the control group. According to the self-report questionnaire that Dr. Pahnke developed to measure the depth of a mystical experience, 9 out of the 20 subjects reported a mystical experience. After data analysis, the blind was uncovered and Dr. Pahnke learned that 8 out of the 9 subjects who had experienced a mystical experience were from the psilocybin group while only 1 was from the control group. Dr. Pahnke’s conclusion was that psilocybin was able to catalyze a mystical experience in religiously-inclined subjects who took psilocybin in a religious context. At the six-month follow-up, the subjects reported that their psilocybin-induced mystical experiences had had lasting benefits.¹⁶⁷ Dr. Pahnke’s conclusion, that psilocybin can facilitate mystical experiences that have long-lasting benefits, has held up under the scrutiny of a twenty-five year follow-up study with the original subjects conducted by this author.¹⁶⁸

Throughout 1961 and 1962, Dr. Leary and associates administered a series of psilocybin experiences to prisoners inside Concord Prison, with the goal of reducing their rate of recidivism. No special regulations governed research with prisoners, unlike current regulations which recognize that the special circumstances imposed by the loss of freedom make the ability of prisoners to give fully uncoerced consent to participate in research highly unlikely.¹⁶⁹ ¹⁷⁰ Though Dr. Leary widely reported the claim that his experimental team had dramatically reduced recidivism and criminal behavior in the group of prisoners to whom they administered psilocybin,¹⁷¹ ¹⁷² ¹⁷³ this claim was shown to be false and misleading by a thirty-four year follow-up study of the criminal justice system records of

¹⁶⁷Pahnke W, Richards W. Implications of LSD and Experimental Mysticism. *J Relig Health* 5 (1966): 399-429.

¹⁶⁸Doblin R. The Good Friday Experiment- A twenty-five year follow-up and methodological critique. *J Transpers Psych* 23 (1991) 1:1-28.

¹⁶⁹45 CFR 46, Subpt. C (1998).

¹⁷⁰The ability of children to give their informed consent is also suspect. Special regulations govern the participation of children in research studies. 45 CFR 46, Subpt. D.; 34 CFR 97, Subpt. D (1998).

¹⁷¹Leary T, Metzner R. Use of psychedelic drugs in prisoner rehabilitation. *Brit J Soc Psychi* 2 (1968): 27-51.

¹⁷²Leary T. The effects of consciousness-expanding drugs on prisoner rehabilitation. *Psyched Rev* 10 (1969): 20-44.

¹⁷³Metzner R. Reflections on the Concord Prison Project and the Follow-up Study. *J Psychoact Drugs* 30 (1998) 4:427-428.

the original subjects, also conducted by this author.¹⁷⁴

Throughout the later half of 1962, Drs. Leary and associates began the process of building an independent base of financial and organizational support that was not formally affiliated with Harvard. By October 1962, they had established a non-profit foundation called the International Federation for Internal Freedom (IFIF) and began seeking members and donations.¹⁷⁵

ERA OF GROWING CONCERN — 1962-1964

1962 Kefauver-Harris Amendments to the 1938 Food, Drug, and Cosmetic Act

Efforts to enhance the powers of the FDA had been developing in Congress for several years prior to the passage of the 1962 Kefauver-Harris Amendments to the 1938 Food, Drug, and Cosmetic Act. The primary focus of Senator Kefauver's hearings on the regulation of the pharmaceutical industry, initiated in 1959, had been on the high price of medicines, with a secondary focus on giving FDA power to review the efficacy of drugs as well as their safety.¹⁷⁶ According to an FDA document, "The original impetus for the effectiveness requirement was Congress's growing concern about the misleading and unsupported claims being made by pharmaceutical companies about their drug products, coupled with high drug prices."¹⁷⁷ Efforts to require manufacturers to prove the efficacy of their products were opposed by AMA, which held the view that, "a drug's efficacy varies from patient to patient. Hence any judgement concerning this factor can only be made by an individual physician who is using the drug to treat an individual patient."¹⁷⁸

In the early 1960s, news came to the United States from Europe, Japan and Canada of thousands of babies born with severe birth defects caused by the prescription drug Thalidomide, prescribed to pregnant women for morning sickness but still under test in the United States.¹⁷⁹ The fear generated by these reports, and the fact that the company

¹⁷⁴Doblin R. Dr. Leary's Concord Prison Experiment: A 34-Year Follow-up Study. *J Psychoact Drugs* 30 (1998) 4:419-426.

¹⁷⁵Though the first newsletter of IFIF was dated May 1963 (Vol. 1, #1), the initial statement of purpose and appeal for members of IFIF was dated October 31, 1962.

¹⁷⁶Wardell W, Lasagna L. *Regulation and Drug Development*. Washington, DC American Enterprise Institute for Public Policy Research, 1975: 14.

¹⁷⁷See FDA Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products: 2. <http://www.fda.gov/cder/guidance/1397fnl.pdf>

¹⁷⁸Wardell, Lasagna: 14.

¹⁷⁹In 1962, President Kennedy awarded the President's Distinguished Federal Civilian Service Award, the highest civilian honor available to government employees, to Dr Frances Kelsey, the FDA official who held up the approval of Thalidomide by asking for more information on safety.

that sought to market Thalidomide in the United States had already distributed over two million doses in the United States for investigational use, helped catalyze public and Congressional support for the increased regulation of drugs.¹⁸⁰

In 1962, the Kefauver-Harris Amendments to the 1938 Food, Drug, and Cosmetic Act were passed and resulted in a major expansion of FDA authority.¹⁸¹ The 1938 Act had required that premarket tests demonstrate a drug's safety but had not required a demonstration of a drug's efficacy. The 1962 Amendments required that FDA approval for marketing could be obtained only if data from "adequate and well controlled investigations" provided sufficient evidence demonstrating that new drugs were both safe and effective.¹⁸²

The 1962 Amendments further shifted the balance of power between the FDA and the pharmaceutical industry by requiring the pharmaceutical companies to obtain premarketing approval from FDA, instead of simply requiring them to submit data to FDA in the context of premarketing notification. According to the 1938 Amendments, when manufacturers submitted data about the safety of their product to FDA as part of a New Drug Application (NDA), FDA had 60 days to respond. If FDA did not respond, the substance was considered approved for marketing. FDA could respond fairly easily, however, simply by raising questions about safety, as Dr. Kelsey did about Thalidomide. The Amendments eliminated the automatic approval of NDA's if FDA did not respond within any time limit and required that the FDA give explicit approval of all NDA's prior to the commencement of marketing.¹⁸³ A target of 180 days was specified but no penalties were imposed on FDA for responding after 180 days had passed.¹⁸⁴ FDA also obtained the authority to withdraw already approved drugs from the market if they didn't meet the new efficacy standards or if there were new data or concerns about safety.¹⁸⁵

In order to demonstrate effectiveness, pharmaceutical companies were required to conduct clinical trials in humans, while FDA received the authority to regulate the clinical testing of new drugs in human subjects.¹⁸⁶ As a regulatory tool, FDA created a new document, the Investigational Exemption to the New Drug Application (IND), which researchers were required to obtain before human experimentation could be initiated.¹⁸⁷

¹⁸⁰<http://www.fda.gov/cder/about/history/page31.htm>

¹⁸¹87 P.L. 781; 76 Stat. 780, October 10, 1962.

¹⁸²Sec. 102 (a) 1 and Sec 102 (a) 2 (d) 5 of the Act.

¹⁸³Sec. 104 (b) of the Amendment, amending Sec. 505 (c) of the Act.

¹⁸⁴Sec. 104 (c), amending Sec. 505 (c) of the Act.

¹⁸⁵Sec. 102 (2) (e) of the Amendment, amending Sec. 505 (e) of the Act.

¹⁸⁶Sec. 103 (b) of the Act. FDA now had explicit authority to require that, 1) preclinical animal studies demonstrating safety be conducted prior to the initiation of human studies, 2) clinical investigators sign statements agreeing that they or investigators responsible to them would supervise all patients receiving the test drug and that the drug would not be supplied to other investigators, 3) records of the research data collected be established, maintained and submitted for review.

Only researchers who were “experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs” would be permitted to use unapproved drugs for experimental purposes.¹⁸⁸ In order to obtain an IND, sponsors of clinical research (usually pharmaceutical companies or government research agencies) were required to submit to FDA a signed statement from each investigator describing the researcher’s qualifications and protocol design (plan of investigation).¹⁸⁹ Sponsors needed to provide FDA and the investigators with “full information concerning the preclinical investigations that justify clinical trials, together with fully informative material describing any prior investigations and experience and any possible hazards, contraindications, side-effects, and precautions to be taken into account in the course of the investigation.”¹⁹⁰ Regulations established by FDA after the 1962 Amendments provided that if FDA did not respond within 30 days after sponsors submitted IND applications requesting permission to conduct research, the IND applications were to be considered approved.¹⁹¹

In the view of economist Dr. Henry Grabowski, in the decade and a half following the passage of the 1962 Kefauver-Harris Amendments to the 1938 Food, Drug, and Cosmetic Act, the introduction of the efficacy requirement was a “major reason for the delays and decline in the rate of introduction of new drugs...[that] “are safer than the ones they would replace.”¹⁹² He wrote in 1976 that, “One of the bitter ironies of this situation is that the 1962 amendments were spurred by an alarm over the safety of new drugs – by the fears created by the thalidomide incident.”¹⁹³

Protections for human subjects were also formally mandated for the first time, within the context of the 1962 Amendments.¹⁹⁴ Researchers were required to fully inform their subjects that they were to receive an investigational drug and had to obtain their formal consent. As part of the IND application, researchers needed to certify in writing that they had obtained “the consent of the subjects, or their representatives, except where this is not

¹⁸⁷Drayer, Burns: 255.

¹⁸⁸Sec 102 (d) 6 of the Amendment, amending Sec. 505 (d) of the Act.

¹⁸⁹The form that researchers needed to sign was entitled, “Procedural and Interpretative Regulations: New Drugs For Investigational Use,” and was formally known as Form FD 1573. According to the form, FDA’s authority was derived from “section 505 (i) of the Federal Food, Drug, and Cosmetic Act and Sec. 130.3 of Title 21 of the Code of Federal Regulations.”

¹⁹⁰Part 4 (a) of Form FD 1573.

¹⁹¹21 CFR 312.40 (b).

¹⁹² Grabowski H. *Drug Regulation and Innovation- Empirical Evidence and Policy Options*. Washington, DC: American Enterprise Institute for Public Policy Research, 1976: 3. The issue of the speed of the drug review process is discussed in more detail in Chapter 3.

¹⁹³*Ibid.*, 2.

¹⁹⁴Sec 103 (b) of the Amendment, amending Sec. 505 (i) of the Act.

feasible, or in the investigator's professional judgement, is contrary to the best interests of the subjects."¹⁹⁵ The requirement in the 1962 Amendments that subjects be fully informed of the experimental nature of the study and formally consent to participate were essentially the same as the voluntary standards contained in the Nuremberg Code. The fundamental change brought about by the 1962 Amendments, but not by the Nuremberg Code, was that the application process for seeking prior governmental approval for the testing of experimental drugs in humans included the requirement that researchers certify in writing that their subjects would be fully informed and would give their consent to participate in the research project.

The 1962 Amendments and Psychedelic Research

FDA's new authority had a dramatic impact on the conduct of psychedelic research. Neither Sandoz Pharmaceuticals nor any other entity attempted to present FDA with evidence from "adequate and well controlled investigations" proving that psychedelics had been demonstrated safe and effective for the treatment of any clinical indication. As a result, LSD, psilocybin and mescaline and all other psychedelic drugs, though still legal, were considered to be experimental, unapproved drugs for which FDA permission was required before human administration could take place. The direct provision of psychedelics to physicians by pharmaceutical companies outside of the newly created IND process was no longer permitted. Psychedelics could no longer be administered as part of a research or treatment program not linked to a federally- approved research project, even if the physician thought his or her prior experience showed that the drugs could be used safely and could be effectively administered to patients. From 1963 on, psychedelic drugs were to be supplied only to researchers who either worked within federal or state agencies or obtained grants or permission from such agencies.¹⁹⁶

The End of the Harvard Research Project

In response to the passage of 1962 Amendments, Robert Barrigar, a Harvard Law School student sympathetic to the goals of the Harvard psychedelic research team, conducted and then published a detailed legal analysis of the wording of the 1962 Amendments. He sought to determine "the legal limitations on the distribution and use (including experimental use) of psychedelic drugs, and the constitutionality of such limitations."¹⁹⁷ The conclusion of his analysis was that the Amendments did indeed cover psychedelic research, and that it was necessary for psychedelic researchers to come into compliance with the new FDA regulations. Though not noted in the paper, the FDA was authorized to grant "selected exemptions" to the regulations to CIA and military research, which it did with virtually no oversight.¹⁹⁸

¹⁹⁵Part 4 (g) of Form FD 1573.

¹⁹⁶Grinspoon L, Bakalar J. *Psychedelics Reconsidered*. New York: Basic Books, 1979: 309.

¹⁹⁷Barrigar R. The Regulation of Psychedelic Drugs. *Psyched Rev*1 (1964) 4:394.

Rumors had surfaced in early 1962 that members of Dr. Leary's research team were providing psychedelics to Harvard undergraduates. Whether or not the initial rumors were true, in February 1962, an article in the Harvard Crimson by then undergraduate Andrew Weil reported that undergraduates had indeed been able to obtain access to psilocybin from members of the research team.¹⁹⁹ The provision of LSD and psilocybin to Harvard undergraduates generated substantial opposition from the Harvard administration and other Harvard faculty, and became one of the primary factors that led to the 1963 departures of Drs. Leary and Alpert from Harvard. The growing dissatisfaction of Drs. Leary and Alpert with the strict requirements of rigorous scientific research as well as their enthusiastic participation in the growing exploration of psychedelics by leading lights in the non-academic world were also contributing factors in their departure.

The impact of the new Federal regulations was described in a May 1963 report from the Harvard psychedelic research team, after it was clear that Drs. Leary and Albert were leaving Harvard. According to the report, "There is, however, with the exception of the Federal government, no research being performed with LSD and related psychedelic substances. The reason is simple: since the enactment of the new-drug laws on February 8, 1963, there has been no sponsor for LSD or psilocybin. We at IFIF [International Federation for Internal Freedom] are at present devoting most of our time, effort and money in the attempt to become an FDA-approved sponsor...As soon as such sponsorship is established, IFIF will be authorized to purchase LSD and psilocybin from Sandoz Pharmaceuticals and distribute them at cost to the physicians in their respective research groups. Each group, therefore, must obtain, complete, and return the required form FDA 1573."²⁰⁰

IFIF did not become an FDA-approved sponsor of psychedelic research. After Drs. Leary and Alpert left Harvard in May 1963, psilocybin research was continued for several years afterwards by Dr. Pahnke at the Harvard-affiliated Massachusetts Mental Health Center, within carefully designed and FDA-approved research protocols.^{201 202}

¹⁹⁸Lee, Schlain: 92.

¹⁹⁹Weil A. Better Than a Damn. *The Harvard Crimson*(Feb 20, 1962): 2. see also Weil A. Alpert Defends Drugs on 'Open End.' *The Harvard Crimson* (May 27, 1963): 1, 6; Weil A. Investigation Unlikely in Dismissal of Alpert. *The Harvard Crimson*(May 29, 1963): 1.

²⁰⁰Staff. Supplies. *IFIF Newsletter* 1 (May 1963) 1:1.

²⁰¹Pahnke W, Salzman C, Katz R. Report on a Pilot Project Investigating the Psychopharmacological Effects of Psilocybin in Normal Volunteers. Self-published, November 1, 1966. The purpose of this research was "1. to determine the most useful control substance for use with Psilocybin, 2. to ascertain the feasibility of a double-blind experimental procedure with Psilocybin and an active control substance, and 3. to determine the most suitable route of administration."

²⁰²Pahnke (1967): 60-84.

1964 Declaration of Helsinki

The development of a formalized and enforced set of protections for human subjects took another step forward in 1964, when a series of international meetings of the World Medical Assembly culminated in the Declaration of Helsinki.²⁰³ The Declaration of Helsinki contained principles similar to those stated in the Nuremberg Code and made mandatory in the 1962 Amendments, principles such as the requirement that the risks to subjects be fully disclosed, be balanced by potential benefits, and that participation in research be voluntary, with subjects retaining the right to opt out of the experiment at any time with no penalty.

The primary new protection contained in the Declaration of Helsinki was the provision that all researchers submit their protocols to independent review bodies, which later became known as Institutional Review Boards (IRB). The purpose of the IRBs was to conduct an independent evaluation of the likely risks to the human subjects resulting from their participation in the proposed experiment.²⁰⁴ ²⁰⁵ ²⁰⁶ Though not in itself legally binding in the United States, the Declaration of Helsinki led in relatively short order to regulations that established IRBs as an essential element in human research.²⁰⁷

Apparent Cessation of CIA Psychedelic Research

The Nuremberg Code, the 1962 Amendments, and the Declaration of Helsinki all contained provisions contrary to the conduct of the CIA and US military-funded psychedelic research projects in which unwitting subjects were used.²⁰⁸ These formalized

²⁰³Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, and as revised by the 29th World Medical Assembly, Tokyo, Japan, 1975.

²⁰⁴Basic Principles 2) The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

²⁰⁵HHS regulations governing IRB's can be found at 45 C.F.R. §§ 46.101-46.124 (1998). FDA regs are at 21 C.F.R. pts. 312, 314. The independence of IRBs has been questioned by Professor Jay Katz, who played a role in developing the federal regulation. He submitted testimony to Congress in 1994 outlining his concerns. 1) "the majority of IRB members are on the faculty of the institutions to which the investigators belong." 2) "The funding of research protocols is an important source of revenue for the institutions." 3) "Private, non-local IRBs are being used more frequently by pharmaceutical companies." Katz J. Problems in Securing Informed Consent of Subjects in Experimental Trials of Unapproved Drugs and Devices. Testimony before the U.S. House Subcommittee on Regulation, Business Opportunities, and Technology of the Committee on Small Business, (May 23, 1994):125-35.

²⁰⁶Federal Policy for the Protection of Human Subjects, 53 FR 45,660 and 45,665-66 (November 10, 1988).

²⁰⁷Levine R. *Ethics and Regulation of Clinical Research-2nd Edition*. Baltimore: Urban and Schwarzenberg, 1986: 321-363.

codes of conduct increased the moral, legal, financial and political risks to the government of conducting such studies. These increased risks, coupled with the largely disappointing results of the mind-control research into the potential uses of the classic psychedelics (LSD, psilocybin and mescaline) as brain-washing, interrogation and non-lethal incapacitants, apparently led the CIA to halt its in-house psychedelic research programs with the classic psychedelics, though not before the full spectrum of potential covert uses for these drugs had been well characterized. In any case, CIA researchers had already succeeded in developing more effective “superhallucinogens” such as BZ,²⁰⁹ which actually did cause hallucinations, impaired motor control for prolonged periods of time, and worked well as a non-lethal incapacitant.^{210 211}

Psychedelic Research Shortly Before the Shutdown

A substantial scientific momentum had been generated during the period of open acceptance of psychedelic research. Some tantalizing findings had been reported with the use of psychedelics in the treatment of alcoholism,²¹² in the treatment of pain and psychological distress in cancer patients,²¹³ in the treatment of post-traumatic stress

²⁰⁸Other research subjects in U.S. military-funded research were exposed to nuclear radiation without their consent. See Frankel M. *The Times of My Life and My Life with the Times*. New York: Random House, 1999.

²⁰⁹Brecher E and the editors of Consumer Reports. *Licit and Illicit Drugs*. Mount Vernon, New York: Consumers Union, 1972: 349. For a fascinating movie in which BZ plays a prominent role, see Jacob’s Ladder, starring Tim Robbins.

²¹⁰Rumor has it that BZ would have been delivered as a mist during the ill-fated rescue of the American hostages at the Embassy in Tehran, if the helicopters had got that far. BZ might have profoundly disoriented Iranian militants and American hostages alike, perhaps causing everyone exposed to the mist to fall to the ground, unable to handle weapons or take purposive action. BZ would supposedly have permitted the rescue team to pick and choose the hostages from among the militants in relative safety.

²¹¹Though the CIA apparently stopped its research efforts into the use of psychedelics as chemical warfare agents in the mid-1960s, the South African Defence Force (SADF) maintained a chemical and biological warfare programme that in 1992 is reported to have manufactured a ton of MDMA for use in crowd control. Evidence was presented at the South African Truth Commission that this MDMA was dumped into the sea in 1993, shortly before South Africa became a signatory to the international chemical weapons convention. However, evidence from South African police indicates that this MDMA was probably exported to Europe for sale on the illicit market. see Bothma S. Search On For Ecstasy Capsules. *Business Day (Johannesburg)*, November 8, 1999.

²¹²Mangini M. Treatment of Alcoholism Using Psychedelic Drugs: A Review of the Program of Research. *J Psychoact Drugs*30 (1998) 4:381-418.

²¹³Kast E. Attenuation of anticipation: a therapeutic use of lysergic acid diethylamide. *Psychiat. Quart.* 41 (1967): 646-657. Abstract “LSD has profound and incisive impact on the mental and antonomic

disorder in concentration camp survivors,²¹⁴ as an adjunct to psychotherapy for neurosis, anxiety and depression,^{215 216 217} to enhance group therapy with an emphasis on ego enhancement,²¹⁸ as catalysts for creativity,²¹⁹ and with the use of psychedelics as chemical tools to help researchers better understand psychosis and schizophrenia.²²⁰ As reported by Grinspoon and Bakalar, "Between 1950 and the mid-1960s there were more than a thousand clinical papers discussing 40,000 patients, several dozen books, and six international conferences on psychedelic drug therapy. It aroused the interest of many psychiatrists who were in no sense cultural rebels or especially radical in their attitudes. It was recommended for a wide variety of problems including alcoholism, obsessional neurosis, and childhood autism."²²¹

Despite the positive momentum generated by promising findings and a good track record of safety for subjects receiving psychedelics in carefully controlled clinical settings, apparatus of human beings. It has aroused widespread interest in various fields, and the search for new and therapeutic uses continues. This study explores the therapeutic possibilities of LSD in the treatment of the painful terminal stages of serious disease. “

²¹⁴Bastiaans J. Mental Liberation Facilitated by the use of Hallucinogenic Drugs. in Grinspoon L, Bakalar J. (eds.) *Psychedelic Reflections*. New York: Human Sciences Press, 1983: 143-152.

²¹⁵Sherwood J, Stolarof M, Harman W. The Psychedelic Experience--A New Concept in Psychotherapy. *J Neuropsychi* 4 (1962) 2:69-80. Also, Mogar R, Savage C. Personality Changes associated with Psychedelic (LSD) Therapy: A Preliminary Report. *Psychother*1 (1964): 154-162.

²¹⁶Leuner H, Holfeld H. Ergebnisse und Probleme der Psychotherapie mit Hilfe von LSD-25 und verwandten substanzen. [Results and problems of psychotherapy assisted by LSD-25 and related substances]. *Psychiat et Neurol (Basel)* 143 (1962): 379.

²¹⁷Leuner H. Psychotherapy with Hallucinogens; A Clinical Report with Special Reference to the Revival of Emotional Phases of Childhood. in Crockett R, Sandison R, Walk, A (eds.) *Hallucinogenic Drugs and their Psychotherapeutic Use*. London: H.K.Lewis, 1963: 67-73.

²¹⁸Abramson H. Lysergic Acid Diethylamide (LSD-25): XIX. As an adjunct to brief psychotherapy, with special reference to ego enhancement. *J Psychol* 41 (1956): 199.

²¹⁹Harman W, McKim R, Mogar R, Fadiman J, Stolaroff M. Psychedelic Agents in Creative Problem-Solving: A Pilot Study. *Psycho Reports*19 (1966) Monograph Supplement 2:211-227. This paper reports on a series of studies conducted at the International Foundation for Advanced Study in Menlo Park, directed by Myron Stolaroff. FDA permission had been obtained for these studies, with the LSD being provided by Sandoz and the mescaline purchased from a chemical supply house. These studies were shut down by the FDA in 1965. This paper is the most recent publication of data from human research in the United States with mescaline.

²²⁰Abramson H, Hewitt M, Lennard H, Turner W, O'Neill F, Merlis S. The stablemate concept of therapy as affected by LSD in schizophrenia. *J Psychol* 45 (1959): 75-84.

²²¹Grinspoon, Bakalar: 192.

the rise of the controversy over the increasing non-medical use of psychedelics was accompanied by pressure on the FDA from an unexpected direction demanding that it close down legitimate research. In an 1964 editorial, Dr. Roy Grinker, the President of the American Medical Association, stated, “The Food and Drug Administration has failed in its policing functions. The drugs are indeed dangerous even when used under the best of precautions and conditions.”²²² Dr. Grinker was concerned that psychedelic researchers could precipitate a psychotic reaction even in “normal” subjects without a clinical diagnosis and promote psychic addiction. These risks were real, but had been taken into account in the data-driven risk/benefit analysis conducted by Dr. Cohen that came to opposite conclusions about the relative dangers of psychedelic research.

ERA OF ALMOST TOTAL PROHIBITION (1965-1989)

Drug Abuse Control Amendments of 1965

By the mid-1960s, psychedelics had thoroughly escaped from the medical research labs and were being used by an ever increasing number of mostly young people, causing substantial public discord. The passage of the Drug Abuse Control Amendments of 1965²²³ presaged the end of the legal use of psychedelics by both non-medical users and medical researchers, though it took about seven years for medical research to dwindle to almost nothing.²²⁴ The Drug Abuse Control Amendments of 1965 were directed against the non-medical use of depressant and stimulant drugs, as well as drugs with an “hallucinogenic effect,” not including marijuana.²²⁵ ²²⁶ The law stated that no person shall manufacture, compound, process or sell any depressant or stimulant drugs, or any drugs with an “hallucinogenic effect,” except for those people with special permits given for a few restricted uses, primarily legitimate wholesale distribution, research and medical applications. The Department of Health, Education and Welfare (HEW), not the Bureau of Narcotics, was given the responsibility to enforce the law, with HEW delegating the responsibility to FDA.²²⁷ Possession of these drugs “for the personal use of himself or a member of his household,” was still permitted,²²⁸ reminiscent of the absence of penalties

²²²Grinker R. Bootlegged ecstasy. *JAMA* 187 (1964):192.

²²³89 P.L. 74; 79 Stat. 226, July 15, 1965.

²²⁴Staff. FDA Lists Approved LSD Research Projects. *FDA Consum* (Sept 1975): 24-25.

²²⁵Sec 3 (a) of the Act.

²²⁶ Effect of Drug Abuse Control Amendments of 1965 on State laws. 89 P.L. 74, § 10, 79 Stat. 235, provided:“(a) Nothing in this Act [amending this section and enacting this note, among other things; for full classification, consult USCS Tables volumes] shall be construed as authorizing the manufacture, compounding, processing, possession, sale, delivery, or other disposal of any drug in any State in contravention of the laws of such State.

²²⁷Sec 8 (a) of the Act.

for possession of alcohol during Prohibition.²²⁹ Individuals could not, however, manufacture their own drugs for their own personal consumption. Licenses were required to manufacture and were not given for purposes of personal consumption, unless that consumption was in the context of FDA-approved research.²³⁰

As with laws against the non-medical use of opiates and the non-medical use of marijuana, the laws against the non-medical use of psychedelics began to impact medical research. FDA demanded that almost all LSD researchers stop their studies and return their supplies of LSD.²³¹ According to Myron Stolaroff, who was then conducting research with LSD and mescaline, over 50 research projects were shut down by FDA in 1965.²³² The National Institute of Mental Health (NIMH) stopped supplying LSD to some previously approved projects.²³³ In April 1966, Sandoz Pharmaceutical company stopped distributing LSD in the United States.²³⁴ Congressional hearings were held in 1966 regarding the decision of FDA and NIMH to put a halt to most LSD research projects.²³⁵ Senator Robert Kennedy argued strongly for the continuation of research,²³⁶ as did several influential researchers including Drs. Cohen, Szara, Freedman and Dahlberg.²³⁷ At a meeting of the American Psychiatric Association the same month as the Senate Hearing, Dr. Szara remarked, “It is my belief that it would be most unfortunate if we were to permit undue hysteria to destroy a valuable tool of science, and evaporate an eventual hope for the hopeless.”²³⁸ A letter entitled, “Shrouds around LSD,” was published in Science, bemoaning the refusal of FDA and NIMH to support new LSD research protocols.²³⁹

1966 PHS Regulations Requiring IRB Review

On February 8, 1966, the Surgeon General of the United States Public Health

²²⁸ Sec 3 (c) of the Act.

²²⁹ cite no possession penalties in Prohibition.

²³⁰ Sec. 4.

²³¹ Grinspoon, Bakalar: 309.

²³² personal communication, Myron Stolaroff, January 5, 2000.

²³³ Pollard J. Shrouds around LSD. *Science* 154 (1966): 844.

²³⁴ Lee, Schlain: 93.

²³⁵ Organization of Government Programs Related to LSD. Senate Subcommittee on Executive Reorganization Hearing, May 24-26, 1966.

²³⁶ Kennedy, Sen. R. Senate Subcommittee on Executive Reorganization Hearing on Organization of Government Programs Related to LSD. May 24-26, 1966: 63.

²³⁷ Szara S. Are Hallucinogens Psychoheuristic?. *Hallucinogens: An Update*. NIDA Monograph Series #146, Washington, DC, NIH Publication #94-3872, 1994: 33-51.

²³⁸ Szara S. The hallucinogenic drugs- curse or blessing? *Am J Psychiatry* 123 (1967):1517.

²³⁹ Pollard J. Shrouds around LSD. *Science* 154 (1966): 844.

Service promulgated the first federal regulation requiring IRB review for all “new, renewal, or continuation research or research training grants in support of clinical research and investigation involving human subjects.” On July 1, 1966, this requirement was extended to all USPHS-funded projects.²⁴⁰

The need for review and approval of scientific research protocols by an independent board of reviewers in addition to the FDA required researchers to develop a wider network of support among their institutional colleagues, both those currently on the IRB as well as those who might rotate onto the IRB in the future. As psychedelic research grew more controversial, such support became more difficult to obtain. Though it slowed and in some cases effectively prevented psychedelic research, the newly mandated IRB process was an important attempt to ensure that protocols for all human research were refined, improved and made safer for the subjects.

1967 Cessation of NIMH Funded Psychedelic Research

In 1967, a joint committee of FDA and NIMH, the Psychotomimetic Advisory Committee, was established to review all protocols for psychedelic research.²⁴¹ Shortly after the establishment of the Committee, NIMH ended all in-house psychedelic research projects.²⁴²

1967 Single Convention on Narcotic Drugs

In 1967, the United States formally adopted the Single Convention on Narcotic Drugs, an international treaty which had been negotiated in 1961 but was not ratified in the US until 1967.²⁴³ Marijuana, opiates, and cocaine were all covered by the Single Convention, psychedelics were not.²⁴⁴ The Single Convention required that signatory countries harmonize their domestic controls over the manufacturing, distribution, and uses of drugs originally placed under control by the Convention.²⁴⁵ Additional drugs could be subsequently placed under control of the Single Convention by the Commission on Narcotic Drugs of the Economic and Social Council of the United Nations, after reviewing

²⁴⁰Curran W. Government Regulation of the Use of Human Subjects in Medical Research: The Approaches of Two Federal Agencies. in *Experimentation with Human Subjects*, ed. P.A. Freund. New York: George Braziller, 1970: 436.

²⁴¹Grinspoon, Bakalar: 311.

²⁴²Lee, Schlain: 93.

²⁴³Single Convention on Narcotic Drugs (US Treaty Series Vol. 520, US Treaties and other International Agreements. Vol 18 Part 2, 1967, p. 1407-1431.), which concluded on March 30, 1961, and entered into force in the United States on June 24, 1967. For the text of the treaty, see http://www.incb.org/e/ind_ar.htm

²⁴⁴Article 2, Substances Under Control, and attached Schedules.

²⁴⁵Article 4, General Obligations.

recommendations made by the World Health Organization.²⁴⁶ The Single Convention created the International Narcotics Control Board (INCB) to be the administrative and supervisory entity within the World Health Organization to manage the continued operation of the treaty.²⁴⁷

Medical research was not forbidden for any of the drugs covered by the Single Convention.²⁴⁸ One of the general obligations of the signatories was stated as follows: “Subject to the provisions of the Convention, to limit exclusively to medical and scientific purposes the production, manufacture, export, import, distribution of, trade in, use and possession of drugs.”²⁴⁹ The Convention required prescriptions for the medical use of controlled drugs.²⁵⁰ One limitation on the extent of research that can take place with Schedule I drugs is that Signatories must report to the Board on an annual basis the amount of Schedule I drugs that will be used each year for medical and scientific purposes. However, supplementary estimates may be provided during the year with an explanation as to the need for additional supplies.²⁵¹

Penalties for violations of the Convention consist primarily of the International Narcotic Control Board (INCB) calling attention to the failings of the Party in public forums. The harshest possible action that the Board could take would be to call on the other Parties, the Commission of Narcotic Drugs, and the Economic and Social Council of the United Nations to take action to “stop the import of drugs, the export of drugs, or both,

²⁴⁶Article 3, Changes in Scope of Control.

²⁴⁷Article 5, The International Control Organs, and Article 9, Composition and Functions of the Board. According to the INCB in its 1999 Annual Report issued on February 23, 2000 (http://www.incb.org/e/ind_ar.htm), “The Board consists of 13 members who are elected by the Economic and Social Council and who serve in their personal capacity, not as government representatives. Three members with medical, pharmacological or pharmaceutical experience are elected from a list of persons nominated by the World Health Organization (WHO) and 10 members are elected from a list of persons nominated by the Members of the United Nations and by States parties that are not Members of the United Nations, in accordance with article 9 of the 1961 Convention as amended by the 1972 Protocol. Members of the Board are persons who, by their competence, impartiality and disinterestedness, command general confidence. The Council, in consultation with the Board, makes all arrangements necessary to ensure the full technical independence of the Board in carrying out its functions.”

²⁴⁸Article 2, Substances Under Control, Section 5 (b) stated, “A Party shall, if in its opinion the prevailing conditions in its country render it the most appropriate means of protecting the public health and welfare, prohibit the production, manufacture, export and import of, trade in, possession or use of any such drug except for amounts which may be necessary for medical and scientific research only, including clinical trials therewith to be conducted under or subject to the direct supervision and control of the Party.”

²⁴⁹Article 4, 1(c).

²⁵⁰Article 24. Limitation on Production of Opium for International trade.

²⁵¹Article 19. Estimates of Drug Requirements.

from or to the country or territory concerned, either for a designated period or until the Board shall be satisfied as to the situation in that country or territory.”²⁵² The Council may if it sees fit bring the matter to the attention of the General Assembly.²⁵³ The requirements of the Single Convention make it seem very difficult for a non-governmental organization to establish a medical marijuana production facility. However, the Convention goes on to say that, “The Agency shall, in respect of opium [or marijuana], have the exclusive right of importing, exporting, wholesale trading and maintaining stocks *other than those held by manufacturers of opium [or marijuana] alkaloids, medicinal opium [or marijuana] or opium [or marijuana] preparations.* Parties need not extend this exclusive right to medicinal opium [or marijuana] and opium [or marijuana] preparations.”²⁵⁴ It thus is possible under the provisions of the Single Convention for a private, non-governmental organization to obtain permission from a Party to grow marijuana for licensed medical uses without the Party coming into violation of any of the provisions of the Convention. The non-governmental producer would not need to sell its output to the Agency and could distribute its stocks for medical purposes to the extent that it was licensed to do so. However, in order for a non-governmental producer to function in this manner, the Agency would need to extend formally its exclusive rights to manufacture and trade marijuana for medical purposes to the non-governmental entity.

The 1997 approval by Great Britain’s Home Office of the production of marijuana plants for medical purposes by GW Pharmaceuticals provides evidence that parties to the Single Convention can indeed permit the cultivation of marijuana for medical purposes by non-governmental entities.²⁵⁵ However, GW Pharmaceuticals is not actively seeking to develop the medical use of the marijuana plant but is producing the plant to develop marijuana extracts and non-smoking delivery systems.²⁵⁶ Nevertheless, the Single Convention does not prohibit the cultivation of marijuana for purposes of research into the medical uses of the whole smoked plant. The 1999 Annual Report of the INCB contained no objections to the decision of the Home Office to permit GW Pharmaceuticals to produce the marijuana plant for medical purposes.²⁵⁷

William Scholten, senior policy advisor, Ministry of Health, Welfare and Sport, Department of Pharmaceutical Affairs, has reported that in 1999, the Dutch government

²⁵²Article 14. Measures by the board to ensure the execution of provisions of the convention.

²⁵³Article 14 (1) (d).

²⁵⁴Article 23 2(e).

²⁵⁵See website of GW Pharmaceutical company’s non-profit arm, the UK Medicinal Cannabis Project: <http://www.medicinal-cannabis.com/project/main.html>

²⁵⁶The goal of GW Pharmaceuticals as stated on its website is the development of “non-smoked prescription cannabis-based medicines.”

²⁵⁷Report of the INCB for 1999. http://www.incb.org/e/ind_ar.htm

began the process of establishing its own government agency to produce and distribute marijuana for clinical research, in full accordance with all its obligations under the Single Convention.²⁵⁸ The Dutch government intends to license non-governmental entities to produce marijuana for medical purposes but has no intention of extending its exclusive right to stock or distribute the output. Rather, “the growers will need a contract and a license, and within four months after harvesting they will have to sell it to the agency... the agency will develop preparations in cooperation with manufacturers and investigators.”²⁵⁹
260

The Canadian government is also moving forward to license the production of a smokable form of marijuana for medical research purposes. On May 5, 2000, Health Canada issued a Request for Proposal (RFP) seeking a non-governmental supplier to establish “ a Canadian source of quality, standardized, affordable, research-grade marijuana. The requirement for a domestic source is outlined in Health Canada's Research Plan for Marijuana for Medicinal Purposes, released June 9, 1999, by Health Minister Allan Rock. Health Canada aims to have a five-year contract in place by this summer.”²⁶¹
262

²⁵⁸Scholten W. Legal Aspects on Medicinal Use of Hemp:Historic Overview and Present Policy of the Netherlands. in *Drug Infor J34* (2000): 329-332. Mr. Scholten is Senior Policy Advisor, Ministry of Health, Welfare and Sport, Department of Pharmaceutical Affairs, The Hague, The Netherlands.

²⁵⁹*Ibid.*, 332.

²⁶⁰In an April 4, 2000 letter from Dutch Health Minister Dr. Els Bors to the Chairman of the Health Committee (vaste commissie voor Volksgezondheid, Welzijn en Sport), Dr. Bors reported that staff members are currently being sought for the Dutch governments' medical marijuana agency. An accompanying commission will also be installed. All procedures will be in accordance with international drug conventions. Clinical trials and product development will follow. Institutions that are already working in this area, like Weleda Nederland NV in Zoetermeer, Stichting Patientenbelangen Medicinale Marihuana and Maripharm in Rotterdam will eventually be included in this process. Dr. Henk van Wilgenburg, Dr. Adele van der Plas, Nevil Schoenmaker and Mario Lap have created the "Foundation for Cannabis Genetics", aiming at delivering suitable Cannabis to the Cannabis Agency. (Sources: Letter of Els Borst of 4 April 2000 <http://www.parlement.nl/doc/rec/hfdframe/rec001.htm>, Email of Mario Lap of 22 April 2000).

²⁶¹Health Canada News Release 2000-44. May 5, 2000. Health Canada to establish source of research-grade marijuana. http://www.hc-sc.gc.ca/english/archives/releases/2000/2000_44e.htm

²⁶²Research Plan for Marijuana for Medicinal Purposes: A Status Report. Therapeutic Products Programme, Health Canada, June 9, 1999. 1-10. According to the document, “The Commission of Narcotic Drugs General Assembly has resolved under the United Nations 1961 Convention that countries, including Canada, should refrain from the proliferation of supply sources and avoid unforeseen imbalances caused by sales of seized or confiscated drugs and products manufactured from such drugs. The long standing policy of the organization overlooking treaties compliance is that countries should not base a licit activity (i.e. research) on an illicit source. Consequently, the idea of recycling marijuana seized in enforcement activities

1968 Establishment of the DOJ's Bureau of Narcotic and Dangerous Drugs

In 1968, the Department of Health Education and Welfare (HEW), through the FDA's Bureau of Drug Abuse Control, lost the authority to prosecute the non-medical use of psychedelic and certain other drugs. The FDA's Bureau of Drug Abuse Control was combined with the Department of Treasury's Bureau of Narcotics into the Bureau of Narcotic and Dangerous Drugs (BNDD), under the authority of the Department of Justice.

Marijuana Research

According to Dr. Norman Zinberg, Harvard Medical School, "Unfortunately, there was very little research on the medical usefulness of marijuana between 1934 and the late 1960s."²⁶³ In 1967, in order to generate scientific data to understand better the consequences of the widespread non-medical use of marijuana by young people, Dr. Andrew Weil, Harvard Medical School, applied for FDA permission to conduct a basic safety study of the human use of marijuana. Dr. Weil's study, though not directly related to marijuana's medical uses, was designed to gather basic safety data necessary to evaluate marijuana's medical as well as non-medical uses.²⁶⁴ Though substantial pressure had been placed on FDA to restrict psychedelic research, in 1967 FDA did permit Dr. Weil's study with marijuana. The approval of Dr. Weil's study suggests that the attitudes of FDA officials toward marijuana research were not uniformly negative, and that external pressure against marijuana research was not overwhelming.

Overwhelming External Pressure Against Psychedelic Use and Research

In his 1968 State of Union Address, President Lyndon Johnson addressed the non-medical use of psychedelics and other substances. He warned Americans against "these powders and pills which threaten our nation's health, vitality and self-respect."

In 1968, the American Journal of Psychiatry published an article reporting how the increasingly negative media coverage of the effects of psychedelics was contributing to difficulties in recruiting subjects for studies and in retaining permission to conduct research with those few projects still permitted.²⁶⁵ A special series of articles about psychedelic and marijuana users, all based on research funded by NIH, FDA and/or NIMH grants,

is not a viable option. Securing a licit source will ensure that the marijuana used in medical research is of an acceptable, standardized quality, free from fungi, molds, pesticides or other contaminants.": 9.

²⁶³Zinberg N in ed. Randall R. *Cancer Treatment and Marijuana Therapy*. Washington, DC: Galen Press, 1990: 16.

²⁶⁴Weil A, Zinberg N, Nelson J. Clinical and Psychological Effects of Marijuana in Man. *Science* 162 (1968): 1234-1242.

²⁶⁵Dahlberg C, Mechaneck M, Feldstein S. LSD Research: The impact of lay publicity. *Amer J Psychiat* 125 (1968) 5:137-141.

concluded with an editorial noting the cyclical nature of lay and scientific interest in psychedelics, seemingly predicting an imminent conclusion of this area of research.²⁶⁶

Though scientific research with psychedelics was almost entirely stopped through a combination of regulation, cessation of federal and other sources of funding, and social pressure on researchers, members of Institutional Review Boards and potential subjects, the non-medical use of LSD continued to spread. Psychedelics became an integral part of the lifestyles of a substantial number of leaders and members of what came to be called “the counterculture.” As a response to the considerable amounts of drug abuse and social turmoil that Federal officials attributed to the non-medical use of LSD, an Amendment to the Food, Drug, and Cosmetic Act was passed on October 24, 1968 criminalizing possession of LSD,²⁶⁷ which the Drug Abuse Control Amendments of 1965 had not done.

On March 6, 1969, Dr. Morris Lipton, Chairman, Preclinical Psychopharmacology Research Review Committee, National Institute of Mental Health, wrote a letter to Surgeon General Stewart expressing concern about the stifling impact on scientific research that he feared the proposed new drug legislation working its way through Congress would create. Dr. Lipton wrote, “Most disturbing to us are the proposed licensing procedures. These will apparently call for scientific investigators of submit their research protocols for approval [by BNDD] in order to gain permission to work with those high-abuse liability drugs... We hope the Council will concern itself with the possible consequences of the proposed law and try to minimize its potentially deleterious effects upon research in the field of psychopharmacology.”²⁶⁸

In July 1969, LSD researchers Drs. Humphry Osmond and Bernard Aaronson wrote,

“The very brief banning of LSD-25 research in 1966 was a classic example of precipitate, unintelligent action springing from high government levels. Since then, some research has been restored to a limited degree, but expansion has not been greatly encouraged, nor is an atmosphere of panic and politicking conducive to clear thinking, planning and diligent, long-continued inquiry.”²⁶⁹

²⁶⁶Cohen S. The Cyclic Psychedelics. *Amer J Psychiat*125 (Sept 1968) 3:149-150, concluding “LSD, STP and Marijuana: Special Section.”, 97-150.

²⁶⁷LSD and other Depressant and Stimulant Drugs, Possession Restriction. 90 P.L. 639; 82 Stat 1361. Oct 24, 1968.

²⁶⁸Lipton M. Appendix. *Psychotomimetic Drugs- Proceedings of a Workshop organized by the Pharmacology Section, Psychopharmacology Research Branch, National Institute of Mental Health, held at the University of California, Irvine, on January 25-26, 1969.* Workshop Series of Pharmacology Section, National Institute of Mental Health No 4. Efron D (ed.). New York: Raven Press, 1970: 351.

²⁶⁹Aaronson B, Osmond H. Psychedelics and the Future. *Psychedelics- The Uses and Implications of Psychedelic Drugs*, eds. Aaronson B, Osmond H. Garden City, New York: Anchor Books, 1970: 471.

Controlled Substances Act of 1970

In 1970, Congress passed the Controlled Substances Act to provide a context within which to regulate both the medical and the non-medical uses of drugs.²⁷⁰ The Controlled Substances Act repealed all prior drug control laws and replaced them with a comprehensive and unified law.²⁷¹ Among other provisions, the Act established a set of five schedules into which all drugs subject to control were categorized, with different degrees of control for each schedule. Psychedelics were placed in the most restrictive Schedule I, along with heroin, marijuana and other drugs considered to have “high abuse potential,”²⁷² “no currently accepted medical use in treatment,”²⁷³ and “lack of accepted safety for use under medical supervision.”²⁷⁴ The responsibility to set quotas for the production of Schedule I substances was given to the Attorney General.²⁷⁵ While the prescription use of Schedule I drugs was not permitted, nothing in the Controlled Substances Act prevents the FDA from approving research with or eventually reclassifying any Schedule I drug as a prescription medicine.^{276 277}

The Controlled Substances Act added a requirement that researchers seeking to study Schedule I drugs register and be approved by the Bureau of Narcotic and Dangerous Drugs, later to become the Drug Enforcement Administration (DEA).²⁷⁸ In addition,

²⁷⁰91 P.L. 513; 84 Stat. 1236. October 27, 1970.

²⁷¹Sec. 701. Repeals and Conforming Amendments.

²⁷²Sec. 202 (b) (1) (A).

²⁷³Sec. 202 (b) (1) (B).

²⁷⁴Sec. 202 (b) (1) (C).

²⁷⁵Sec. 306.

²⁷⁶Hutt P, Merrill, R. Prescription Drug Controlled Substances. *Food and Drug Law: Cases and Materials-Second Edition, University Casebook Series*, Westbury, New York:Foundation Press, 1991: 535-536. They state, “Nonetheless, although the requirements established under the Controlled Substances Act may impose extra burdens upon manufacturers, physicians and pharmacists, they do not prevent FDA from approving an NDA for any controlled substance that has a legitimate medical use.”

²⁷⁷One reader wondered if a would-be exporter could attack the Schedule I status of a drug in a foreign country if that drug had already been rescheduled in its home country, claiming the foreign Schedule I status as a barrier to trade without scientific justification, citing the Uruguay Round. It is doubtful that a would-be exporter of any approved medicine, even if not scheduled, could force the regulatory agency of another country to accept its drug for prescription use without first having to satisfy the regulatory requirements of the country in which it seeks to sell the drug. The Global Harmonization of Technical Requirements (International Conference on Harmonization) does make it somewhat easier to submit foreign data for review, but it in no way implies that approvals in one country must automatically and immediately be approved in other countries.

²⁷⁸Sec. 303 (b). The following factors are to be considered: 1) maintenance of effective controls against diversion, 2) compliance with applicable State and local laws, 3) prior conviction record of applicant under

recordkeeping requirements were established for the manufacture and distribution of scheduled drugs.²⁷⁹ DEA's primary responsibility in licensing physicians to conduct research was to ensure that Schedule I drugs used in FDA-approved research projects would not be diverted to non-medical uses either by the researchers themselves or their subjects. In order to reduce diversion by researchers, DEA granted licenses to handle Schedule I drugs only to physicians that it determined were trustworthy (the absence of a criminal record involving drugs was the main test) and required that detailed records be kept of the distribution of all supplies. By virtue of its authority to control the non-medical use of drugs, the DEA can legitimately raise issues of protocol design related to diversion, such as studies proposing to administer take-home supplies of Schedule I drugs. This might be an issue in marijuana research, but not in psychedelic research, since psychedelics are administered under the direct supervision of a therapist. Protocol design issues related to the scientific merit of the study remain the responsibility of FDA.

The Controlled Substances Act does empower the Secretary of Health, Education and Welfare to set standards for the treatment of narcotic addicts.²⁸⁰ The term "narcotic" is defined by the Act as opium, cocaine "or any compound, manufacture, salt, derivative or preparation thereof."²⁸¹ Standards for research into the treatment of narcotic addicts are still under the control of the FDA. While this authority has been used by HHS primarily to regulate the use of methadone and LAAM for treating heroin addicts, this section of the Act gives HHS the authority to regulate the practice of medicine with all drugs that may become approved by the FDA to treat narcotic addicts, including the psychedelics.

One psychedelic drug, ibogaine, has been patented for the treatment of withdrawal in people dependent on narcotics,²⁸² for the treatment of dependence on cocaine,²⁸³ tobacco,²⁸⁴ alcohol,²⁸⁵ and poly-drug dependence.²⁸⁶ Phase I FDA-approved research

Federal or State laws relating to manufacture, distribution of dispensing of such substances, and 4) such other factors as may be relevant to and consist with the public health and safety. With just a few exceptions, physicians have generally not had a difficult time obtaining DEA licenses to conduct FDA-approved research with Schedule I drugs. Sec. 304 related to the denial, revocation or suspension of the license.

²⁷⁹Sec. 307 and Sec. 308.

²⁸⁰Sec. 4. "The Secretary of HEW, after consultation with the Attorney General and with national organizations representative of persons with knowledge and experience in the treatment of narcotic addicts, shall determine the appropriate methods of professional practice in the medical treatment of the narcotic addiction of various narcotic addicts, and shall report thereon from time to time to Congress."

²⁸¹Sec. 102 (16).

²⁸²Lotsof H. Rapid Method for Interrupting the Narcotic Addiction Syndrome. U.S. Patent 4,400,496. Filed Nov. 18, 1983, and granted Feb. 12, 1985..

²⁸³Lotsof H. Rapid method for Interrupting or Attenuating the Cocaine and Amphetamine Abuse Syndrome. U.S. Patent 4,587,243. Filed July 15, 1985, and granted May 6, 1986.

with ibogaine has been initiated in subjects with a former but not current cocaine dependence (to be discussed in Chapter 2). After the passage of the Controlled Substances Act, LSD research was conducted with some success in the treatment of heroin addicts (to be discussed soon). If any psychedelics do eventually become approved by the FDA for the treatment of heroin or cocaine addicts, the legal authority to micromanage the practice of medicine already rests with HHS. The medical practice of the use of psychedelics for the treatment of alcoholics, or people addicted to nicotine, marijuana or any other drug, would not be subject to extensive regulation by HHS unless additional legislation were passed.

External Pressure for Medical Marijuana Research

In 1972, anecdotal reports began to circulate claiming that marijuana was effective in the treatment of nausea associated with cancer chemotherapy.²⁸⁷ Harvard Medical School Drs. Sallen, Zinberg, and Frei applied for and obtained FDA permission to conduct a study into the use of THC, the main psychoactive ingredient in marijuana, in cancer patients. Dr. Zinberg testified about FDA's approval of the use THC but not marijuana in this study, remarking, "We used THC instead of marijuana because it would have been impossible to get a marijuana protocol approved. As it was, it took two years of consistent effort to get a THC protocol approved. If we would have tried to use smoked marijuana, it would have taken forever."²⁸⁸ The Sallen, Zinberg, and Frei study generated mildly promising results, suggesting that THC could be somewhat helpful in reducing nausea in cancer chemotherapy patients. They also reported that several patients dropped out of the study because smoked marijuana worked so much better for them than THC.²⁸⁹

According to Dr. Zinberg, by 1972, overwhelming external pressure had been placed on FDA not to approve scientific research into the possible beneficial uses of smoked marijuana. This pressure was probably related at least in part to a May 1972 petition filed by the National Organization for the Reform of Marijuana Laws (NORML) with the Bureau of Narcotic and Dangerous Drugs, requesting that marijuana be reclassified to make it into a legal prescription medicine. Several months later, BNDD

²⁸⁴Lotsof H. Rapid Method for Interrupting or Attenuating the Nicotine/Tobacco Dependency Syndrome, U.S. Patent #5,026,697, filed May 30,1990, and granted June 25, 1991.

²⁸⁵Rapid Method for Attenuating the Alcohol Dependency Syndrome, U.S. Patent # 4,857,523, Filed July 18, 1988, and granted Aug. 15,1989.

²⁸⁶Rapid Method for Interrupting or Attenuating Poly-Drug Dependency, U.S. Patent 5, 152,994, filed May 31, 1990 and granted Oct. 6, 1992.

²⁸⁷Grinspoon L, in Randall R. *Cancer Treatment and Marijuana Therapy* Washington, DC: Galen Press, 1990: 5.

²⁸⁸Zinberg N, in Randall R: 14.

²⁸⁹Sallen S, Zinberg N, Frei F. Antiemetic Effect of Delta-9-Tetrahydrocannabinol in Patients Receiving Cancer Chemotherapy. *New Eng J Med*293 (1975): 785-797.

rejected the petition without hearing, claiming the US International Treaty obligations prevented such a reclassification.²⁹⁰ NORML filed suit in the D.C. Court of Appeals, winning on January 15, 1974 the first in a long series of decisions in an ultimately unsuccessful twenty-year effort to force the rescheduling of marijuana through means other than FDA-approved research and NDA approval.²⁹¹

Expanding Federal Regulation of Human Research/DHEW Rules and the Belmont Report

A series of additional Federal regulations protecting human subjects became effective on May 30, 1974.²⁹² These rules codified regulations that had been originally proposed in 1966 by the Department of Health, Education and Welfare (DHEW). Among other things, these rules, known as the National Institutes of Health (NIH) Policies for the Protection of Human Subjects, governed various aspects of the actions and composition of the local Institutional Review Boards (IRB). These new regulations were promulgated in order to enhance the ability of IRBs to serve as a major regulatory device by which human subjects would be protected from undue risks. IRBs, though subjected to detailed regulation by the Federal government, were composed of members of local institutions. Providing this added layer of oversight was considered the responsibility of the local institutions, which were not reimbursed for the costs involved in staffing these Boards.

Several months after the DHEW rules became effective, the passage of the National Research Act in July 1974²⁹³ established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.²⁹⁴ The purpose of the Commission was to “(i) conduct a comprehensive investigation and study to identify the basic ethical principles which should underlie the conduct of biomedical and behavioral research involving human subjects, (ii) develop guidelines..., (iii) make recommendations to the Secretary [HEW]...”²⁹⁵ After extensive deliberations over the course of several years, the Commission issued its final report in 1978, which came to be known as the Belmont

²⁹⁰37 FR 18093 (September 1, 1972).

²⁹¹National Organization for the Reform of Marijuana Laws (NORML) v Ingersoll, 497 F.2d 654 (D.C. Cir. 1974). The court determined that the international treaties do not categorically prohibit the possible rescheduling and medical use of marijuana or any other Schedule I drug. NORML’s case ended in May 1992, when the DEA was finally able to articulate a rational basis acceptable to the DC Court of Appeals for the decision to deny NORML’s request for the rescheduling of marijuana. Other than by a direct act of Congress, the conclusion of NORML’s case means that FDA NDA approval remains the only route by which marijuana can become rescheduled into a prescription medicine.

²⁹²Department of Health and Human Services Rules and Regulations, 45 CFR 46.

²⁹³National Research Act, 93 P.L. 348; 88 Stat. 342. July 12, 1974.

²⁹⁴National Research Act, Title II, Protection of Human Subjects of Biomedical and Behavioral Research. Sec. 201 (a).

²⁹⁵ National Research Act. Sec. 202 (1) A.

Report.²⁹⁶

The Belmont Report did not, however, lead directly to the creation of a consensus about appropriate ethical standards for research or to new regulations. According to Dr. Robert Levine, “FDA, through its regulatory proposal of August 8, 1978, notified all concerned of its intentions to disregard both the letter and the spirit of the Commission’s recommendations on IRBs...and quite promptly DHHS began to violate both the letter and the spirit not only of the Commission’s recommendations but also of the National Research Act’s clear directions as to how and when it was to respond to the Commission’s recommendations.”²⁹⁷

The issues discussed in the Belmont Report subsequently became the focus of the President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, which met from 1980-1983.²⁹⁸ Regulations were promulgated in 1983 and 1989, but it was not until 1991 that a uniform set of guidelines governing human research were codified for 16 federal agencies that conduct or sponsor such research.²⁹⁹

The Last Bastion of Psychedelic Research

After the NIMH stopped its support of intramural psychedelic research in 1967, the largest research team that continued investigating the clinical use of psychedelics was directed by Dr. Albert Kurland and was located at the Maryland Psychiatric Research Center in Spring Grove, Maryland.³⁰⁰ Dr. Kurland had established and directed the

²⁹⁶The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research: The Belmont Report; Ethical Principles and Guidelines for the Protection of Human Subjects of Research. DHEW Publication No (OS) 78-0012, Appendix I, DHEW Publication No (OS) 78-0013, Appendix II, DHEW Publication No (OS) 78-0014, Washington, 1978.

²⁹⁷Levine R. *Ethics and Regulation of Clinical Research-2nd Edition*. Baltimore: Urban and Schwarzenberg, 1986, xii (preface).

²⁹⁸The President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research: Implementing Human Research Regulations: The Adequacy and Uniformity of Federal Rules and of their Implementation. U.S. Government Printing Office, Stock No. 040-000-00461-1. Washington, DC, 1983.

²⁹⁹Federal 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 (June 18, 1991), Food and Drug Administration, Protection of Human Subjects; Informed Consent; Standards for Institutional Review Boards for Clinical Investigations 21 CFR Parts 50 and 56.

³⁰⁰Yensen R, Dryer D. Thirty Years of LSD Research: The Spring Grove Experiment and its Sequels. in (eds.) Schlichting M, Leuner, H. *Worlds of Consciousness. Vol 5 Abstracts and Selected Papers from the 1st International Congress of the European College for the Study of Consciousness (ECSC), Göttingen, Germany, September 24-27, 1992*. Berlin: Verlag für Wissenschaft und Bildung, 1995:141-176.

Maryland Psychiatric Research Center and obtained funding for his psychedelic research by using a portion of general research grants for the entire center that he obtained from pharmaceutical companies, foundations and government grants. As he remarked, “If anybody had money, we got some of it.”³⁰¹ Dr. Kurland had begun planning the research center in 1959 and had gradually gathered together a stellar team of scientists and support staff. In 1969, Vice President Spiro T. Agnew, ex-Governor of Maryland, officially dedicated the Research Center’s new four-story building. At that time, the staff numbered over 100 people, a substantial number of whom worked on psychedelic research. Dr. Kurland and associates conducted “the largest, most sustained and systematic study of psychedelic drugs and psychotherapy yet attempted.”³⁰² Dr. Kurland’s team conducted studies into the use of LSD, psilocybin, DPT, MDA, DOET and the active placebo Ritalin, in the treatment of schizophrenics, cancer patients,³⁰³ ³⁰⁴ alcoholics,³⁰⁵ heroin addicts³⁰⁶ ³⁰⁷and inpatient³⁰⁸ and outpatient neurotics,³⁰⁹ and also conducted a training program for over 200 mental health professionals. In 1976, despite promising results and hard-won lessons, gradually dwindling political support finally resulted in the termination of Dr. Kurland’s directorship of the Research Center. All the psychedelic research projects were closed down, after over 750 subjects had been treated. According to Richard Yensen, Ph.D, a researcher at the Center, “The majority [of subjects treated] benefited in some way while a minority were unchanged. We are not aware of any long-term complications among the subjects.” ³¹⁰

A 1975 article in the FDA Consumer, FDA’s official magazine, noted “FDA records indicate there have been about 170 legitimate research projects with LSD over the past 10 years, but most are no longer active.”³¹¹ FDA reported that only 5 projects were

³⁰¹personal communication, Dr. Albert Kurland, October 12, 1999.

³⁰²Yensen, Dryer: 141.

³⁰³Grof S, Goodman L, Richards W, Kurland A. LSD-Assisted Psychotherapy in Patients with Terminal Cancer. *Internat Pharmacopsychiat* 8 (1973) 3:129-144.

³⁰⁴Pahnke W, Kurland A, Unger A, Savage C Grof S. The Experimental Use of Psychedelic (LSD) Psychotherapy. *JAMA*212 (1970) 11:1856-1863.

³⁰⁵Kurland A, Unger S, Shaffer J, Savage C. Psychedelic Therapy Utilizing LSD in the Treatment of the Alcoholic Patient: A Preliminary Report. *Am J Psychiat* 123 (1967) 12:1202-1209.

³⁰⁶Savage C, McCabe O. Residential Psychedelic (LSD) Therapy for the Narcotic Addict: A Controlled Study. *Arch Gen Psychiat*28 (1973): 808-814.

³⁰⁷Kurland A. *Psychiatric Aspects of Opiate Dependence*. West Palm Beach: CRC Press, 1978.

³⁰⁸Savage C, McCabe O, Kurland A, Hanlon T. LSD-assisted Psychotherapy in the Treatment of Severe Chronic Neurosis. *J Alt Stat Conscious*1 (1973) 1:31-47.

³⁰⁹Yensen R, Di Leo F, Rhead J, Richards W, Soskin R, Turek B, Kurland A. MDA-Assisted Psychotherapy with Neurotic Outpatients: A Pilot Study. *J Nerv Ment Dis* 163 (1976) 4:233-245.

³¹⁰Yensen, Dryer: 166.

still authorized to administer LSD to patients in 1975. Of those five, three were not active projects. The two that were still active were at Spring Grove and were shut down in 1976.³¹² By 1975, NIDA, then a branch of NIMH, sat on the joint committee with FDA that reviewed psychedelic research protocols, reflecting a shift in federal priorities away from the exploration of potential therapeutic applications toward a concern over non-medical use.

An internal review conducted in 1975 by the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) revealed that from 1953-1973, HEW had funded 116 different studies of LSD involving 1,750 human subjects at a total estimated cost of \$4 million, not including an unknown amount spent on military and CIA studies. The authors noted that at the time the report was written, “ADAMHA does not fund any research involving administration of LSD to humans. This is not a policy, but rather the result of accumulated findings in the field.”³¹³

The implication of the ADAMHA statement was that research died down because psychedelics were not safe or effective, causing scientists to lose interest in psychedelic research. This view has been convincingly contradicted.³¹⁴ In 1992, Dr. Szara, retired Chief, Biomedical Research Branch, National Institute on Drug Abuse, remarked “clinical research with these drugs essentially stopped... [there were] 20 years of deliberate legal neglect and constraints.”³¹⁵ An article in the *FDA Consumer*, written in 1995, also reflected on the cessation of LSD research as being due to external overwhelming political

³¹¹Staff. FDA Lists Approved LSD Research Projects. *FDA Consum* (September 1975): 24-25.

³¹²Two of the projects listed were at Spring Grove and were shut down in 1976. One project listed was at Langley Porter Neuropsychiatric Institute, San Francisco, California, another was at Vista Hills, in San Francisco. According to Dr. Reese Jones (personal communication, October 11, 1999), who worked at Langley Porter in 1975 and is still there, “Technically we had an old IND still active on the FDA approved list around that time but had long since stopped giving any LSD but our IND had nothing to do with chronic users or therapy. Their [Vista Hills] medical director was Keith Ditman... They may well have been doing something therapeutic with LSD in the years before 1975 but I would be surprised if the studies were still active in 1975. I think most everyone had stopped by then.” The most recent LSD-related article by Keith Ditman in *Medline* was published in 1970. The last project listed by FDA was a study of psychosis (patients with special problems) at Medical College of Birmingham, Birmingham, Alabama. According to Dr. Jones, “there was someone there interested in LSD but I don't think any human administration was involved by that time.” No LSD research papers from the Medical College of Birmingham were published in the 1970s.

³¹³Report on ADAMHA Involvement in LSD Research, as cited in Szara, Steven. Are Hallucinogens Psychoheuristic? in *Hallucinogens: An Update, NIDA Monograph Series # 146* Washington, DC, NIH Publication # 94-3872. 1994: 39.

³¹⁴Asher J. Whatever happened to Psychedelic Research? *APA Monit* (November 1975): 4-5.

³¹⁵Szara: 38.

pressure:

According to FDA's Klein, [Dr. Michael Klein had come to Pilot Drug from DEA to work on regulatory issues related to drugs of abuse] the Controlled Substances Act was an attempt to control the use of these drugs so that they would be used only for scientific reasons. "The purpose of the act was not to hinder or stop research," he said, "but to ensure that as the research proceeded, proper controls were in place to prevent abuse and misuse of the drugs." However, by the 1970s, psychedelic drugs were not only viewed as a public health problem but also carried a social implication. Psychedelic drugs were associated with "hippies," a counterculture of mostly young people who felt alienated from the mainstream American society and grew, in part, out of the anti-Vietnam war sentiment of the time.^{316 317}

In the same article in the FDA Consumer, Dr. Frank Vocci, NIDA's Director of Medications Development, commented, "There seemed to be an increasing hysteria about hallucinogenic drugs in the 1960s that essentially shut down the research. It became socially unacceptable to do this kind of work."³¹⁸

The most recent paper reporting new results from human research with mescaline was published in 1966.³¹⁹ The most recent US study reporting on the administration of LSD to at least one human subject was published in 1973, from the Spring Grove team.³²⁰ The most recent study reporting on the administration of psilocybin to at least one human subject was published in 1976.³²¹ The latest administration of psilocybin to a subject in

³¹⁶Kurtzweil P. Medical Possibilities for Psychedelic Drugs. *FDA Consum*(September 1995). http://www.fda.gov/fdac/features/795_psyche.html

³¹⁷For insight into the link between "hippies" and psychedelics, see Allen J, West L. Flight from Violence: Hippies and the Green Revolution. *Amer J Psychiat*125 (Sept. 1968) 3:120-126.

³¹⁸ Kurtzweil P. (1995).

³¹⁹Harman W, McKim R, Mogar R, Fadiman J, Stolaroff S. Psychedelic Agents in Creative Problem-Solving: A Pilot Study. *Psychol Reports* 19 (1966) Monograph Supplement 2:211-227.

³²⁰Savage C, McCabe O. Residential Psychedelic (LSD) Therapy for the Narcotic Addict: A Controlled Study. *Arch Gen Psychiat* 28 (1973) 6:808-814. After the Center was shut down, Drs. Kurland, DiLeo, and Yensen, continued to work to keep the psychedelic research project alive. In 1979, they managed to obtain FDA approval for the continuation of the LSD research with terminal cancer patients. Lack of funding and no institutional support hampered their ability to conduct the study, which was abandoned in the early stages without generating any data.

³²¹Parashos A. The psilocybin-induced "state of drunkenness" in normal volunteers and schizophrenics. *Behav Neuropsychiat* 8 (1976 Apr-1977 Mar) 1-12:83-6.

any FDA-approved study took place in 1978, under the direction Dr. Ron Siegel, who was researching visual hallucinations.³²²

In 1997, Dr. Torsten Passie published a complete international bibliography of books, chapters, and peer-reviewed articles about psychedelic and psycholytic (low dose) psychotherapy with any psychedelic drug, covering from 1931-1995 and including 687 entries.³²³ The most recent listing of new data from a US-conducted psychedelic research project published in a peer-reviewed journal was from 1979, based on research that took place at Spring Grove before 1976.³²⁴

Cessation of European Psychedelic Research

Psychedelic research was just shut down not only in the United States, but around the world as well. The October 1999 Medline search on LSD showed that the most recent foreign study was published in 1975, from Czechoslovakia.³²⁵ After 1975, only three European studies in which psychedelics were administered to humans were permitted to continue. Two studies with LSD were conducted in the Netherlands, one by Dr. W. Arendsen Hein³²⁶ who treated 'neurotic' patients in his clinic Veluweland at Ederveen until his retirement in 1977.³²⁷ The second study was conducted by Dr. Jan Bastiaans, who

³²²Personal communication, Ron Siegel, Ph.D., February 20, 2000. See Siegel R. *Hallucinations. Scient Amer* 237 (1977):132-140; also Siegel R, West. L (eds.) *Hallucinations: behavior, experience, and theory*. New York: Wiley, 1975; and Siegel R. *Fire in the brain :Clinical tales of hallucination*. New York: Dutton, 1992.

³²³Passie T. *Psycholytic and Psychedelic Therapy Research 1931-1995: A Complete International Bibliography*. Hannover: Laurentius Publishers, 1997.

³²⁴Berendes M. Formation of Typical Dynamic Stages in Psychotherapy Before and After Psychedelic Drug Intervention. *J Alt Stat Conscious* 5 (1974) 4:325-338.

³²⁵The following two publications from 1973 are both from the Spring Grove team. Soskin R. The use of LSD in time-limited psychotherapy. *J Nerv Ment Dis* 157(1973) 6:410-9. Savage C, McCabe O. Residential psychedelic (LSD) therapy for the narcotic addict. A controlled study. *Arch Gen Psychiat* 28 (1973) 6:808-14. The foreign study is: Hausner M. The psychotogenic 'double-blind' model in psycholysis. Case study contribution to the sociogenic theory of schizophrenia. *Psychother Psychosom* 25 (1975) 1-6:26-8.

³²⁶Arendsen Hein G. Dimensions of Psychotherapy. in Abramson H. (ed.) *The Use of LSD in Psychotherapy and Alcoholism*. New York: Bobbs Merrill, 1967: 561-568. This is Arendsen Hein's last publication of research findings. He published his final statement on psychedelics in 1972. Arendsen Hein G. Selbsterfahrung and Stellungnahme eines Psychotherapeuten [Self-Experience and Statement of a Psychotherapist]. in Josuttis M, Leuner H (eds.) *Religion und die Droge*. Stuttgart:Kohlhamme, 1972:96-108.

³²⁷Snelders S. LSD en de psychiatrie in Nederland (Ph.D.-dissertation Vrije Universiteit, Amsterdam 1999).

occasionally administered relatively low to moderate doses of LSD to a small number of concentration camp survivors.³²⁸ Dr. Bastiaans' continued approval to work with LSD in concentration camp survivors until his retirement on January 1, 1988 was due in part to support from politically connected ex-resistance members whom he had treated, and to a patient population that stirred a compassionate reaction among Dutch regulators. Dr. Bastiaans proved unable to locate and train a successor interested in trying to continue the LSD-therapy, which in any case the Dutch government was not likely to permit after Dr. Bastiaans' retirement.³²⁹ Unfortunately for the scientific record, Dr. Bastiaans focused on treatment and not research, and did not generate much in the way of data documenting the results of his treatments.³³⁰ ³³¹

Dr. Hanscarl Leuner in Gottingen, Germany was the only other European researcher permitted to continue to administer low doses of psychedelics (but not LSD) to a small number of subjects until his retirement in 1986.³³² Dr. Leuner was one of the central psychedelic research pioneers in Europe. He originally researched the therapeutic use of low doses of LSD and had earned the substantial respect of German regulators. As a result, his permission to administer certain psychedelics was not withdrawn.

MDMA Research and the FDA

By 1976, all US-based human research with psychedelics had been stopped and all psychedelics considered to be drugs of abuse had been criminalized by Federal authorities. Around this time, a new and still legal psychedelic drug known as MDMA (Ecstasy) began to be used quietly by a small number of psychiatrists and psychotherapists in their clinical practices.³³³ MDMA was a unique molecule that had not been specifically made illegal, but was similar in structure and effect to MDA, a Schedule I drug that had been studied in the 1960s and early 1970s as an adjunct to psychotherapy, with promising results.³³⁴ MDMA

³²⁸Bastiaans J. The KZ Syndrome: A Thirty Year Study of the Effects on Victims of Nazi Concentration Camps. *Revista medico-chirurgicata a societatii de medici si naturalis li diu Jasi* 78 (1974): 573-578.

³²⁹personal communication, Stephen Snelders, November 22, 1999.

³³⁰Bastiaans J. Mental Liberation Facilitated by the Use of Hallucinogenic Drugs. in Grinspoon L, Bakalar J. (eds.). *Psychedelic Reflections*. New York: Human Sciences Press, 1983: 143-152.

³³¹Ossebaard H, Maalste N. The Bastiaans Method of Drug-Assisted Therapy: A Preliminary Follow-up study with former clients. *BullMAPS* 9 (1999) 2:3-9. <http://www.maps.org/news-letters/v09n2/09203maa.html>

³³²Passie T. In Memoriam. *Bull MAPS* 6 (1996) 4:20-21. <http://www.maps.org/news-letters/v06n4/06408mem.html>

³³³Stolaroff M. *The Secret Chief: Conversations With a Pioneer of the Underground Psychedelic Therapy Movement*. Charlotte, North Carolina: Multidisciplinary Association for Psychedelic Studies, 1997.

³³⁴Naranjo C, Shulgin A, Sargent T. Evaluation of 3,4-Methylenedioxymethamphetamine (MDA) as an Adjunct to Psychotherapy. *Medicine et Pharmacologia Experimentalis* 17 (1967): 359-364. Yensen R,

was considered by the clinicians who chose to work with it to have remarkable therapeutic potential due to its relatively short and gentle action, the lack of major perceptual and cognitive alterations that in other psychedelics can contribute to panic attacks and “bad trips,” and the relative ease with which the altered state can be remembered and integrated into daily life so as to anchor long-term change.³³⁵ Of all the psychedelics, MDMA seemed like the substance with the greatest chance of becoming accepted by mainstream psychiatry. Nevertheless, the psychiatrists and psychotherapists working with MDMA at that time did not seek to obtain FDA-permission to conduct research. Dr. Greer believed that the lack of preliminary animal toxicity data would make FDA approval impossible.³³⁶ Some potential researchers were dissuaded by the long-standing regulatory opposition to psychedelic research, others feared that seeking permission for research would bring MDMA to the attention of the federal authorities, hastening its criminalization..

Psychotropic Substances Act of 1978

In 1978, Congress passed the Psychotropic Substances Act.³³⁷ This Act expanded the substances under international control to include central nervous system stimulants (amphetamines), sedative-hypnotics (barbiturates) and hallucinogens (psychedelics). The Act brought the United States into compliance with the International Convention on Psychotropic Substances, which the US had signed in 1971 and which Congress ratified in 1980.³³⁸

As did the Single Convention on Narcotic Drugs, the International Convention on Psychotropic Substances explicitly permitted medical and scientific research with, and possible prescription use, of any drug controlled under the Convention.³³⁹ In places, the language of the Convention on Psychotropic Substances is somewhat more restrictive than the Single Convention, for example preceding medical use with the words, “very limited.”³⁴⁰

Dileo F, Rhead J, Richards W, Soskin R, Turek I, Kurland A. MDA-assisted psychotherapy with Neurotic Outpatients: A Pilot Study. *J Nerv Ment Dis* 163 (1976) 4:223-245.

³³⁵Greer G, Tolbert R. Subjective Reports of the Effects of MDMA in a Clinical Setting. *J Psychoact Drug* 18 (1986) 4:319-327.

³³⁶personal communication, Dr. George Greer, June 2, 2000.

³³⁷Psychotropic Substances Act of 1978, 95 P.L. 633; 92 Stat. 3768. November 10, 1978.

³³⁸The Convention on Psychotropic Substances. US Treaty Series. Vol. 1019, US Treaties and other International Agreements. Vol 32 Part 1, 1979-80: 543-571.

³³⁹Article 5, “Limitation of use to medicinal and scientific purposes.”

³⁴⁰Article 7 (a) of the Convention on Psychotropic Substances states, “In respect of substances in Schedule I, the Parties shall: (a). prohibit all use except for scientific and very limited medical purposes by duly authorized persons, in medical or scientific establishments which are directly under the control of their

The Convention also permitted the manufacture of Schedule I substances for medical purposes by entities that are licensed by the Party.³⁴¹ Nothing in the Convention forbade a Party from granting a license to a governmental agency or a non-governmental, commercial entity to produce marijuana or any other substance for medical research and use.³⁴²

England's Home Office has claimed that the International Convention on Psychotropic Substances, unlike the Single Convention, forbids signatories from independently rescheduling a Schedule I drug covered by the International Convention into a prescription medicine. According to the Home Office, the International Convention requires a collective decision to reschedule by the parties to the Convention.³⁴³ This view is not supported by any text contained in the Convention. Actually, the Convention provides mechanisms for countries to report changes in laws concerning drugs under the jurisdiction of the Convention,³⁴⁴ and for addressing conflicts between control measures required by the Convention and those actually in place within any country.³⁴⁵ Furthermore, the range of enforcement mechanisms available to the International Narcotics Control Board, the supervisory body that manages the implementation of the Convention, is quite limited should any country decide to adopt policies that directly contravene elements of the Conventions.³⁴⁶ Thus, the Home Office's stated position seems one of domestic

Governments or specifically approved by them." Sec 109 of the Psychotropic Substances Act of 1978 notes, " Article 7 of the Convention on Psychotropic Substances shall not be construed to prohibit, or impose additional restrictions upon., research involving drugs or other substances scheduled under the Convention which is conducted in conformity with this subsection and other applicable provisions of this title."

³⁴¹Paragraph (b) of Article 7, "Special provisions regarding substances in Schedule I," states that the parties to the Convention shall, "require that manufacture, trade and distribution and possession be under a special license or prior authorization."

³⁴²Article 8, "Licenses."

³⁴³"Our view of the 1971 Convention is that it does not allow the same latitude in respect of the cannabinoids as the 1961 Convention allows for cannabis. Any unilateral move by the United Kingdom to reschedule the cannabinoids would we believe probably breach the 1971 Convention. The way to achieve a lesser degree of control would thus be through the World Health Organization and amendment of the Convention. " November 16, 1998 letter from A.D. Macfarlane, Home Office, to Dr. Geoffrey Guy, president of GW Pharmaceuticals, a pharmaceutical company with Home Office permission to grow marijuana to manufacture marijuana extracts for medical purposes.

³⁴⁴Article 16, "Reports to be furnished by the Parties."

³⁴⁵Article 19. " Measures by the Board to ensure the execution of the provisions of the Convention."

³⁴⁶For example, Paragraphs 176-177 of the "Report of the International Narcotics Control Board for 1999," contained language stating that the approval in several signatory countries of "drug injection rooms" for IV drug addicts was a violation of the treaty. The INCB took no formal action to seek the closure of

political convenience rather than of international treaty obligation.

Regardless of the views of the Home Office, the policy of the United States is determined by the language of the Psychotropic Substances Act of 1978. The 1978 Act does not forbid rescheduling in the United States prior to such action being taken by the Convention itself. The 1978 Act states “nothing in the Convention shall interfere with ethical medical practice in this country as determined by the Secretary of Health, Education and Welfare [now Health and Human Services] on the basis of a consensus of the views of the American medical and scientific community.”³⁴⁷ The 1978 Act also established specific procedures to be taken in the event of a dispute between the United States and the Convention over the appropriate degree of control to be imposed on any drug.³⁴⁸

Medical Marijuana Research- Positive External Pressure

Throughout the 1970s, public support grew for research into the medical use of marijuana for cancer chemotherapy. From 1973 to 1977, 10 states passed marijuana decriminalization bills, with support for reform cresting in 1977 and eroding from that point onward.³⁴⁹ In 1979, the National Cancer Institute funded and obtained FDA-approval for a small pilot study testing THC and placebo in 15 cancer patients, with smoked marijuana available as a rescue medication for patients who vomited on either the THC or placebo. The study demonstrated that smoked marijuana was more effective for some patients than THC.³⁵⁰ NCI funding and FDA approval of this study were obtained seven years after Dr. Zinberg concluded in 1972 that it was impossible for him to obtain permission for research with smoked marijuana at that time. The approval of the NCI study demonstrated that external pressure in favor of medical marijuana research in cancer patients had become strong enough to overcome internal reluctance and previous external pressure against such research.

From 1978 to 1982, 33 states passed some form of a bill supporting medical

such facilities but instead “encourages Governments to provide a wide range of facilities for the treatment of drug abuse, including the medically supervised administration of prescription drugs in line with sound medical practice and the international drug control treaties, instead of establishing drug injection rooms or similar outlets that facilitate drug abuse.” http://www.incb.org/e/ind_ar.htm

³⁴⁷Sec. 101 (C) (3).

³⁴⁸Sec. 102. When disputes arise, Sec 102 3 (C) (iv) authorizes the Secretary of State to “initiate proceedings to remove the drug or substances from the schedules under the Convention or to transfer the drug or substances to a schedule under the Convention different from the one specified in the schedule notice.”

³⁴⁹Bonnie: 2.

³⁵⁰Chang A, Shiling D, Stillman R, Goldberg N, Seipp C, Barofsky I, Simon R, Rosenberg S. Delta-9-Tetrahydrocannabinol as an Antiemetic in Cancer Patients Receiving High-Dose Methotrexate. *Ann Int Med* 91 (1979): 385-425.

research or medical use of marijuana.³⁵¹ From 1979 to 1983, researchers in five states were able to conduct FDA-approved clinical trials with marijuana and/or oral THC for cancer chemotherapy as a direct result of the medical marijuana bills passed in those states.³⁵² These trials demonstrated that smoked marijuana was more effective for some patients than the oral THC pills, though none of the trials met FDA standards for “adequate and well-controlled” studies demonstrating safety and efficacy.³⁵³ In 1985, after a pharmaceutical company conducted additional trials with just oral THC, FDA approved the oral THC pill for prescription use for the control of nausea associated with cancer chemotherapy.³⁵⁴ No further studies with smoked marijuana were conducted. Public pressure for medical marijuana research was strong enough to get some initial studies conducted but was not strong enough to force the continuation of government-funded research after the oral THC pill was approved as a substitute prescription medicine.

Scheduling of MDMA

From the mid-1970s to 1980, the use of MDMA took place almost entirely within therapeutic contexts, with sessions most frequently conducted in the privacy of homes, offices or the outdoors.³⁵⁵ This use pattern for MDMA took place under the radar of DEA and police authorities. There were no media reports to draw the attention of the authorities nor any of the traditional signs of a developing problem with a new drug, such as emergency room visits linked to the drug as reported by the Drug Abuse Warning Network (DAWN),³⁵⁶ deaths associated with the drug reported by medical examiners,³⁵⁷ or visits to drug treatment centers by people seeking help resolving problems of addiction.

By 1980, MDMA’s then legal status and perceived safety, as well as the strong demand for its subjective effects, began to attract the attention of large scale manufacturers and distributors. By the early 1980s, the use of MDMA shifted to more

³⁵¹Appendix B, in Randall: 337.

³⁵²California, New York, New Mexico, Tennessee and Georgia.

³⁵³Randall R. *Marijuana, Medicine and the Law Volume 2*. Washington, DC: Galen Press, 1989: 346-350.

³⁵⁴FDA approved Marinol for prescription use in the treatment of nausea and vomiting in cancer chemotherapy on May 31, 1985, and for use in the treatment of AIDS wasting syndrome on December 22, 1992.

³⁵⁵Stolaroff M. *The Secret Chief: Conversations With a Pioneer of the Underground Psychedelic Therapy Movement*. Charlotte, North Carolina: Multidisciplinary Association for Psychedelic Studies, 1997.

³⁵⁶When DEA first moved to criminalize MDMA in 1984, the the DAWN system had registered just 8 mentions of MDMA.

³⁵⁷One death had been reported by a Medical Examiner as possibly linked to MDMA but the connection was not conclusive.

“recreational” contexts in public settings in bars and nightclubs, initially in Texas.³⁵⁸ Sales of MDMA were conducted in the open by distributors who used 800 numbers and took payments via credit cards.³⁵⁹ Not surprisingly, this came to the attention of Texas Sen. Lloyd Bentsen, who sat on the Senate Judiciary Committee. Sen. Bentsen urged the Drug Enforcement Administration to take action, which it did in July 1984 when it announced its intention to place MDMA in Schedule I, criminalizing both its medical and non-medical uses.³⁶⁰ In response to DEA efforts to criminalize MDMA, several advocates for the medical use of MDMA successfully requested a DEA Administrative Law Judge hearing on the question of the proper scheduling of MDMA.³⁶¹

DEA also initiated efforts to criminalize MDMA internationally through the mechanisms established by the International Convention on Psychotropic Substances. DEA requested that an Expert Committee operating under the auspices of the World Health Organization evaluate the scientific, epidemiological and drug seizure data on MDMA (and 27 other phenethylamines, of which MDMA was the widely used) and prepare a recommendation concerning bringing MDMA under the control of the provisions of the Convention.³⁶² Dr. Paul Grof, the Chairman of the Expert Committee that met in Geneva from April 22-27, 1985, and other members of the committee responded favorably to information presented to him by proponents of the therapeutic use of MDMA.³⁶³ Though the Committee as a whole recommended that MDMA be placed in Schedule I, the Committee report stated:

No data are available concerning its clinical abuse liability, nature and magnitude of associated public health or social problems, or epidemiology of its use and abuse...The substance has no well defined therapeutic use, but a number of clinicians in the USA have claimed that it is potentially valuable as a psychotherapeutic agent.

³⁵⁸Beck J, Rosenbaum M. *Pursuit of Ecstasy: The MDMA Experience*. Albany: State University of New York Press, 1994.

³⁵⁹*Ibid.*, 19.

³⁶⁰Proposed Placement of 3,4-Methylenedioxymethamphetamine Into Schedule I, 49 FR 30210 (July 27, 1984).

³⁶¹Proposed Placement of 3,4-Methylenedioxymethamphetamine Into Schedule I Hearing, [MDMA, Docket No. 84-48], 49 FR 50732 (December 31, 1984). ACTION: Notice of hearing on proposed rulemaking. This author helped coordinate the efforts of the proponents of MDMA’s therapeutic potential who argued before the DEA that MDMA should be placed in Schedule 3, where it could be prescribed by psychiatrists as a legal medicine.

³⁶²WHO Expert Committee on Drug Dependence. *Twenty-second report. Technical Report Series #729*. Geneva, World Health Organization, 1985.

³⁶³This author went to Geneva to present information to the Expert Committee in February 1985.

It should be noted that the Expert Committee held extensive discussions concerning the therapeutic usefulness of 3,4-methylenedioxymethamphetamine. While the Expert Committee found the reports intriguing, it felt that the studies lacked the appropriate methodological design necessary to ascertain the reliability of the observations. There was, however, sufficient interest expressed to recommend that investigations be encouraged to follow up these preliminary findings. To that end, the Expert Committee urged countries to use the provisions of article 7 of the Convention on Psychotropic Substances to facilitate research in this interesting substance.³⁶⁴

Dr. Grof went further than the Committee and voted against scheduling MDMA. A footnote to the official recommendation from the Expert Committee stated, “One member, Professor Paul Grof (Chairman), felt that the decision on the recommendation should be deferred awaiting, in particular, the data on the substance’s therapeutic usefulness and that at this time international control is not warranted.”³⁶⁵ According to Dr. Grof, it was “very difficult to dissent. The process all the Expert Committees use to make decisions is based on consensus, not voting, so it took some doing to find an appropriate context to register my views.”³⁶⁶ He also noted that the members of the Expert Committees are chosen on the basis of their expertise in substance abuse, that the information available to them is skewed toward harms and is not balanced, and that a recommendation to control the substances that are presented to the Expert Committee is by far the most likely outcome.³⁶⁷

On July 1, 1985, DEA placed MDMA in Schedule I on an emergency scheduling basis.³⁶⁸ MDMA was placed in Schedule I internationally on February 11, 1986, by the United Nations’ Commission on Narcotic Drugs.³⁶⁹

³⁶⁴WHO Expert Committee on Drug Dependence. Twenty-second report: 25.

³⁶⁵WHO Expert Committee on Drug Dependence. Twenty-second report: 25

³⁶⁶personal communication, Dr. Paul Grof, March 20, 2000.

³⁶⁷personal communication, Dr. Paul Grof, March 20, 2000.

³⁶⁸Shulgin A. *Controlled Substances: Chemical and Legal Guide to Federal Drug Laws*. Berkeley: Ronin, 1992: 151. DEA’s emergency scheduling action was subsequently declared illegal in a criminal case because the Attorney General had failed to sub-delegate to DEA the authority to schedule substances on an emergency basis. Kane J. 1986 Memorandum and Opinion. Case No. 86-CR-153 In the United States District Court For The District of Colorado. Pees and Mcneill, Defendants, October 1.

³⁶⁹Woods J. Conclusion. *Drug and Alcohol Dependence: An International Journal on Biomedical and Psychosocial Approaches. Special issue containing papers presented at the Committee on Problems of Drug Dependence Symposium on Stimulants and Hallucinogens, (June/September 1984)*17 (June 1986) 2-3:297-298; also, personal communication, Ms. Valérie Lebaux, Legal Officer, Legal Affairs Sections, United Nations International Drug Control Programme, (UNDCP), March 21, 2000.

Almost two years of testimony led to a DEA Administrative Law Judge recommendation in May 1986 that MDMA be placed in Schedule III, criminalizing its non-medical use but not its medical use.³⁷⁰ The Administrative Law Judge's recommendation was rejected in October 1986 by the DEA Administrator, who placed MDMA in Schedule I effective November 13, 1986.³⁷¹ This ruling was appealed to the DC Court of Appeals by Dr. Lester Grinspoon of Harvard Medical School. In September 1987, the DC Court of Appeals rejected the rationale of the DEA Administrator that he had used to justify ignoring the recommendation of the Administrative Law Judge. The Court remanded the matter back to DEA for reconsideration.³⁷² The DEA Administrator subsequently developed a new rationale and in February 1988, again placed MDMA in Schedule I, effective March 23, 1988, a ruling that was not appealed.³⁷³ As a result, non-medical as well as medical use of MDMA was criminalized in the United States, with legal scientific research possible only with FDA and DEA permission.

Controlled Substance Analogue Enforcement Act of 1986

Though MDMA had somewhat similar subjective effects and was structurally somewhat similar to the psychedelic drug MDA, which had been placed in Schedule I in 1970,³⁷⁴ MDMA could be made illegal only after a lengthy legal process. According to the Controlled Substances Act of 1970, substances could only be scheduled after a rule-making procedure in which the specific substance was evaluated by the Secretary of Health, Education and Welfare according to an 8-factor set of criteria.³⁷⁵ By 1986, the DEA was faced with an increasingly sophisticated group of underground chemists who could relatively easily modify existing scheduled drugs to create new legal drugs with similar effects, and was frustrated by the lengthy process it took to criminalize MDMA. In response to DEA's difficulties, Congress made it easier for DEA to criminalize new substances by passing the Controlled Substances Analogue Enforcement Act of 1986.³⁷⁶

³⁷⁰In the Matter of MDMA Scheduling, Opinion and Recommended Ruling, Findings of Fact, Conclusions of Law and Decision of ALJ, No. 84-48 (Young, ALJ) (May 22, 1986).

<http://www.mninter.net/~publish/mdma.htm>

³⁷¹Lawn J. Schedules of Controlled Substances: Scheduling of 3,4-Methylenedioxyamphetamine (MDMA) into Schedule I of the Controlled Substances Act. 51 FR 36552-36560. (October 14, 1986).

³⁷²Grinspoon v. DEA, 828 F.2d 881 (1st Cir. 1988).

³⁷³Lawn J. Schedules of Controlled Substances: Scheduling of 3,4-Methylenedioxyamphetamine (MDMA) into Schedule I of the Controlled Substances Act. 53 FR 5156 (February 22, 1988).

³⁷⁴Controlled Substances Act of 1970, Sec 202 (c) (c).

³⁷⁵Sec. 201 (c). The only exception, described in Sec 201 (d), was if the U.S. was obligated to control the drug due to international treaty obligations. In those cases, no formal rulemaking process needed to take place.

According to this Act, drugs intended for human use that were substantially similar in structure and effect to drugs that were already in Schedule I or II were considered automatically placed into Schedule I.³⁷⁷ This law has been challenged on the basis of unconstitutional vagueness but has withstood legal challenge.³⁷⁸

Internal FDA Opposition to MDMA Research

In 1986, with the goal of developing MDMA's therapeutic potential through FDA-approved protocols, a non-profit organization opened a Drug Master File for MDMA with data gathered from the standard preclinical animal toxicity studies required by FDA.³⁷⁹ Five different IND applications for permission to conduct research with MDMA were submitted to FDA between 1986 to 1988.³⁸⁰ All five INDs were routed for review to the Division of Neuropharmacologic Drug Products, directed by Dr. Paul Leber, and were placed on Clinical Hold, meaning that they could not be conducted.³⁸¹ Three INDs were

³⁷⁶Anti-Drug Abuse Act of 1986. 99 P.L. 570; 100 Stat. 3207. Oct. 27, 1986. Controlled Substance Analogue Enforcement Act of 1986. 99 P.L. 570, Sec. 1201-1204 ; 100 Stat. 3207-13. Oct. 27, 1986.
³⁷⁷21 U.S.C. §§ 802(32) and 813.

³⁷⁸United States v. Carlson et. al., 87 F. 3d 440 (11th Cir. 1996).

³⁷⁹Data in FDA Drug Master File 6293, held by Multidisciplinary Association for Psychedelic Studies (MAPS).

³⁸⁰The INDs were as follows, 1) Dr. Jonathan Cole, Harvard Medical School. Study intended to evaluate the safety and objective and subjective effects of MDMA in 24 stimulant abusers, administering single oral doses of 75 mgs. and 150 mgs. of MDMA. Subjects would also receive, on separate occasions, 300 mg methaqualone, 20 mg diazepam, 30 mg d-amphetamine and placebo; 2) Dr. Rick Strassman, U. of New Mexico. 20 subject, double-blind active-placebo controlled study using 75-175 mgs of MDMA or 60-120 mg pseudoephedrine, in MDMA-naive subjects; 3) Dr. Enoch Calloway and Dr. Don Wesson, UC San Francisco. 6 subject, double-blind study, using Rorshach and Holtzman projective tests, in medical volunteers (doctors and staff) who are drug-naive. Controls were 10 mg amphetamine and 200 mg amobarbital combination, and inactive placebo; 4) Dr. George Greer. Treatment IND for single patient with cancer who had successfully been treated with MDMA for pain and anxiety prior to the criminalization of MDMA; 5) Dr. Franco Di Leo. Treatment IND for a single patient with unipolar depression who had failed to obtain relief with standard medications.

³⁸¹A June 26, 1992 letter to Dr. Charles Grob from Dr. Lee Zwanziger, Executive Secretary, FDA Drug Abuse Advisory Committee, with background material written by Dr. Curtis Wright, Medical Review Officer of FDA's Pilot Drug Evaluation Staff, discusses four of the rejections by Dr. Paul Leber, Director, FDA Division of Neuropharmacological Drug Products. A fifth application, not mentioned in Dr. Wright's background material, was rejected in a March 5, 1987 letter from Dr. Paul Leber to Dr. Francisco Di Leo, for IND #27,281. The rejection was upheld in a March 18, 1987 letter from Dr. Robert Windom, Assistant Secretary for Health, to Rick Doblin. At the time of the June 26, 1992 letter, responsibility for reviewing MDMA research had been transferred from the Division of Neuropharmacological Drug Products to the

for double-blind controlled trials from researchers at, respectively, Harvard Medical School, UC San Francisco Medical School, and University of New Mexico Medical School. Two INDs were submitted by individual physicians for single case studies, one for a terminal cancer patient who had been successfully treated for pain with MDMA-assisted psychotherapy prior to the criminalization of MDMA and the other for a unipolar depression patient for whom all available treatments had been attempted without success.

FDA based its rationale for rejecting all protocols and single case studies on the hypothetical risk of delayed functional consequences resulting from the possibility of neurotoxicity from MDMA.³⁸² However, MDMA neurotoxicity had not been demonstrated to occur at therapeutic dose levels,³⁸³ while test animals administered multiple high doses of MDMA didn't seem to suffer from adverse functional or behavioral consequences.³⁸⁴ Offsetting the risk of neurotoxicity were proven benefits, with the cancer patient who had been administered MDMA by Dr. Greer when it was still legal to do so reporting clinically significant pain reduction with no problematic side effects.³⁸⁵ The FDA seemed not to be engaging in rational risk/benefit calculations. In another instance, FDA placed greater emphasis on the hypothetical and extremely unlikely possibility of potential brain damage from a single dose of MDMA than on the dire need for treatment in

Pilot Drug Evaluation Staff.

³⁸² June 14, 1988 letter to Dr. Rick Strassman, U. of New Mexico from Dr. Paul Leber, Director, FDA Division of Neuropharmacological Drug Products. Dr. Leber wrote, "We also note that you have written asking our opinion about whether a change in the protocol, limiting your study to terminally ill patients (such as those with AIDS or cancer), would be an acceptable modification leading to eventual removal of the HOLD. We have considered your arguments and do not find them persuasive. Specifically, your argument that the long term toxicity (i.e. potential for serotonergic neuronal brain damage) of MDMA should not be of concern in terminally ill patients, begs the definition of terminal illness. Personally, we are impressed how often medical predictions about the immediacy of death prove wrong. In any case, the protections of law apply to all citizens. Your belief that MDMA offers an advantage to the dying is an insufficient basis to remove that protection."

³⁸³The latest research into MDMA neurotoxicity strongly suggests that the administration of one or several doses to research subjects in a clinical setting offers negligible risk. Vollenweider F, Gamma A, Liechti M, Huber T. Is A Single Dose of MDMA Harmless? *Neuropsychopharm*21 (Oct 1999) 4:598-600.

³⁸⁴The frequent administration of large amounts of MDMA can indeed dramatically reduce serotonin levels in animals, to about 20% of original levels. Even this substantial reduction of serotonin has yet to be linked to significant functional or behavioral consequences. Hatzidimitriou G, McCann U, Ricaurte G. Altered serotonin innervation patterns in the forebrain of monkeys treated with (±)3,4-methylenedioxymethamphetamine seven years previously: factors influencing abnormal recovery. *J Neurosci* 19 (1999) 12:5096-107.

³⁸⁵personal communication, Dr. George Greer, June 7, 2000.

a patient with unipolar depression who had failed to find any relief from any available treatments.³⁸⁶ The FDA rejected a psychiatrist's request to use MDMA in that patient, who had already been prescribed multiple medications as well as two courses of electroshock therapy but was still refusing to eat unless forced.³⁸⁷

All efforts to obtain FDA permission to conduct MDMA research were rejected. In addition to residual external pressure against medical research with drugs whose non-medical use had been criminalized, researchers also faced internal FDA opposition to psychedelic research that seemed based more on the personal prejudices of the reviewers than on scientific risk/benefit estimates. In 1988, the regulatory hurdles at the FDA preventing psychedelic research seemed unlikely to be overcome, or to change anytime soon.

An Opening in Europe

In 1988, several researchers in Europe were able to meet with some limited success. The German Ministry of Health approved a basic safety study in which mescaline would be administered to human subjects, signaling the resumption of psychedelic research in that country.³⁸⁸ In Switzerland, the Ministry of Health permitted a small group of psychiatrists to administer MDMA and LSD-assisted psychotherapy to their patients.³⁸⁹ According to one of the psychiatrists,³⁹⁰ the Ministry drew support for its decision from the report of the 1985 WHO Expert Committee on Drug Dependence that, though recommending that MDMA and 27 other chemically similar compounds called phenethylamines be placed in Schedule I in the International Convention on Psychotropic Substances, also formally "urged countries to use the provisions of article 7 of the Convention on Psychotropic Substances to facilitate research in this interesting substance."³⁹¹

1989 Origins of the International Conference on Harmonization (ICH)

³⁸⁶personal communication, Dr. Franco Di Leo, March 20, 2000.

³⁸⁷personal communication, Mrs. Leona Perlman, June 1986.

³⁸⁸Oepen G, Fuenfegeld M, Harrington A, Hermle L, Botsch H. Right Hemisphere involvement in mescaline-induced psychosis. *Psychiat Res* 29 (1989): 335-336.

³⁸⁹Gasser P. Psycholytic therapy with MDMA and LSD in Switzerland: Follow-up study on the results of Swiss research conducted during 1988-1993. *Bull MAPS* 5 (Winter 1994-95) 3:3-7.

³⁹⁰Personal communication, Dr. Jorg Roth, August 19, 1988.

³⁹¹WHO Expert Committee on Drug Dependence. Twenty-second report: 25. Though obtaining the paragraph in the formal report encouraging research seemed inconsequential at the time, and had no practical effect within the United States, the statement did help facilitate the first regulatory approval of the therapeutic use of MDMA anywhere in the world after MDMA had been criminalized internationally in 1986.

After the passage of the 1962 Amendments and the requirement that pharmaceutical drugs be demonstrated to be both safe and effective, the pharmaceutical drug development process had become increasingly more complex and expensive. Simultaneously, pharmaceutical companies had become more globalized and focused on selling their products in multiple international markets. Complicating the efforts of the pharmaceutical companies to obtain marketing approval for their products in a variety of international marketplaces was the varying processes and regulations imposed by each nation's regulatory agencies.

At its 1989 meeting in Paris, the International Conference of Drug Regulatory Authorities (ICDRA), meeting under the auspices of the United Nation's World Health Organization, first formulated plans for a conference to discuss common scientific and technical aspects of the regulatory review of pharmaceutical products.³⁹² The purpose of the International Conference of Drug Regulatory Authorities (ICDRA), whose first meeting had taken place in 1980, was to promote "harmonization, exchange of information and collaborative approaches to problems which may be of common concern to all drug regulatory authorities."³⁹³

The first steering committee meeting of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) took place in Brussels in April 1990.³⁹⁴ The meeting was hosted by the European Federation of Pharmaceutical Industries' Associations (EFPIA), an organization composed of all major research-based European pharmaceutical companies.

The ICH is an organization with no formal regulatory authority of its own. Over the decade of its existence,³⁹⁵ the ICH has developed a formalized, five-step process of reaching consensus and obtaining implementation³⁹⁶ on four basic categories of issues

³⁹²See website of International Federation of Pharmaceutical Manufacturers Association (IFPMA). *History of the International Conference on Harmonization (ICH)*, <http://www.ifpma.org/ich8.html>

³⁹³See World Health Organization website, International Conference of Drug Regulatory Authorities (ICDRA) <http://www.who.int/medicines/teams/qsm/ICDRA.html>

³⁹⁴The six parties to the first ICH steering committee, each with two seats on the steering committee, included representatives from the pharmaceutical industry and government regulatory agencies, specifically the European Commission of the European Community (EU), EFPIA, Ministry of Health and Welfare, Japan (MHW), Japan Pharmaceutical Manufacturers Association (JPMA), FDA, and Pharmaceutical Research and Manufacturers of America (PhRMA). Observers to the ICH, each with one seat on the Steering Committee, include the World Health Organization (WHO), The European Free Trade Area (EFTA), represented at ICH by Switzerland, and Canada's Drugs Directorate, Health Canada. Two additional seats on the ICH Steering Committee are held by the International Federation of Pharmaceutical Manufacturers Association (IFPMA), which also directs the ICH Secretariat.

<http://www.ifpma.org/ich8.html>

³⁹⁵Four ICH conferences have been held to date, with the fifth scheduled for November 2000.

related to pharmaceutical drug development; safety,³⁹⁷ quality,³⁹⁸ efficacy³⁹⁹ and multidisciplinary.⁴⁰⁰ The authority of the ICH comes only from the voluntary adoption of its guidelines by the national regulatory agencies which participate in the ICH processes. Work toward the development of a Common Technical Document is in process, but whether this ever will or ever should lead to a single international approval process is a matter of substantial controversy.⁴⁰¹

Though the FDA is an active participant in the ICH process, the FDA retains the freedom to adopt or reject any of the guidelines developed by the ICH.⁴⁰² In practice, the FDA has adopted many of the ICH guidelines, and the ICH process and guidelines are having an increasingly important impact on substantive issues related to the research and development of all pharmaceutical products under review by the FDA, including psychedelics and marijuana.⁴⁰³ However, FDA has not obtained and will not obtain any new regulatory authority as a result of its participation in the ICH process.

³⁹⁶Step 1: first proposal for a draft tripartite guideline, Step 2: six parties have agreed on a draft guideline, Step 3: official release for consultation of draft guideline by the three authorities, Step 4: the three authorities have agreed on a final tripartite guideline, Step 5: implementation of harmonized guideline in each region.” Taken directly from a slide from 218/2000 lecture, “Global Harmonization in the Pharmaceutical Industry-2000,” by Brenton James, Worldwide Regulatory Affairs, Glaxo Wellcome, during Tufts Center for the Study of Drug Development’s Postgraduate Course in Clinical Pharmacology, Drug Development and Regulation, Feb 15-18, 2000. Boston, MA.

³⁹⁷ICH guidelines related to safety include S1: Carcinogenicity, S2: Genotoxicity, S3: Kinetics, S4: Toxicity, S5: Reprotox, S6: Biotech Safety, S7: Pharmacology. <http://www.ifpma.org/ich5s.html>

³⁹⁸ICH guidelines related to quality include Q1: Stability, Q2: Analytical Validation, Q3: Impurities, Q4: Pharmacopoeias, Q5: Biotechnology Quality, Q6: Specifications, Q7: GMP. <http://www.ifpma.org/ich5q.html>

³⁹⁹ICH guidelines related to efficacy include E1: Exposure, E2: Clinical Safety, E3: Study Reports, E4: Dose Response, E5: Ethnic Factors, E6: GCP, E7: Clinical Trials in Special Populations-Geriatrics, E8: Clinical Trial Design, General Considerations, E9: Statistical Principles for Clinical Trials, E10: Choice of Control Group, E11: Clinical Investigation of Medicinal Products in the Pediatric Population, E12: Therapeutic Categories. <http://www.ifpma.org/ich5e.html>

⁴⁰⁰ICH guidelines related to multidisciplinary topics include M1: Medical Terminology, M2: Electronic Standards for Transmission of Regulatory Information (ESTRI), M3: Timing of Pre-clinical Studies in Relation to Clinical Trials, M4: The Common Technical Document.

⁴⁰¹lecture by Dr. Brenton James, Professional Course in Clinical Pharmacology, Drug Development and Regulation, Tufts Center for the Study of Drug Development, Boston, MA., February 15- 18, 2000.

⁴⁰²Booth P. FDA Implementation of Standards Developed by the International Conference on Harmonisation. *Food Drug Law J* 52 (1997) 2:203-223.

⁴⁰³Holston S. An Overview of International Cooperation. *Food Drug Law J*. 52 (1997) 2:197-201. When this article was written, Ms. Holston was Deputy Commissioner for External Affairs, FDA.