

CHAPTER 6

REGULATION OF THE PRESCRIPTION USE OF PSYCHEDELICS

As Chapters 1-3 have demonstrated, qualified researchers can obtain regulatory permission both in the United States and abroad to conduct clinical trials investigating the potential medical uses of psychedelics as adjuncts to psychotherapy. As Chapters 4-5 have argued, it is possible to design clinical trials that would be considered “adequate and well controlled” for the evaluation of the medical uses of psychedelics, with the cost of these trials within the range of what can be raised by the non-profit sector. Therefore, large-scale Phase III efficacy trials of psychedelic psychotherapy may eventually be conducted exploring one or more specific clinical indications. If these trials are conducted and do provide sufficient evidence of safety and efficacy, FDA will be faced with the difficult challenge of designing a system to regulate the medical use of psychedelic drugs. For the purposes of this chapter, it will be assumed that one or more psychedelic drugs have been approved by FDA for one or more clinical indications. This chapter will review the regulatory options available to FDA under this scenario and will seek to develop a regulatory framework for the control of psychedelic psychotherapy well in advance of any actual need to do so. This attempt to design an effective regulatory system for psychedelic psychotherapy is being made with the intention of demonstrating that the risks of approving the medical use of a psychedelic drug can be contained so that net benefits to public health can be realized.

Four major areas of concern should be considered in the design of a system for regulating the medical use of a psychedelic drug: misuse (unintentional and/or uninformed), abuse, diversion, and the potential negative effects of information about approved medical use on non-medical use patterns. Misuse occurs when medical professionals unintentionally or negligently deliver psychedelic psychotherapy in a substandard and unskillful manner. Abuse refers to situations in which the medical professionals entrusted with administering psychedelic psychotherapy intentionally do so in an inappropriate manner, for instance to facilitate the sexual abuse of patients.¹³⁰⁴ ¹³⁰⁵ Diversion refers to the illegal transfer of psychedelics intended for medical use to non-medical purposes, either by theft or through the actions of manufacturers, distributors, pharmacists, physicians, medical staff or patients. The effect of information about the prescription use of a psychedelic on non-medical use patterns depends on the extent to which the information is disseminated through advertising and media reports and the impact of that information on non-medical use patterns.

¹³⁰⁴Sadly, this risk is not theoretical. One of the most prominent psychiatrists who worked with MDMA before it was made illegal subsequently lost his medical license as a result of the sexual abuse of several patients while they were under the influence of MDMA or ketamine.

¹³⁰⁵Dehlendorf C, Wolfe S. Physicians disciplined for sex-related offenses. *JAMA* 279 (Jun 17, 1998) 23:1883-8.

The primary mechanisms for control of misuse and abuse by professionals include “professional self-regulation, regulation by the marketplace, governmental regulation (through legislation and the promulgation of [local,] state [and federal] administrative regulations, and tort litigation for professional negligence (“malpractice”).¹³⁰⁶ Diversion is controlled by the Drug Enforcement Administration’s Office of Diversion Control,¹³⁰⁷ and by state authorities such as state medical licensing boards and state law enforcement and investigative personnel.¹³⁰⁸ Advertising about approved drugs is controlled by FDA.¹³⁰⁹ Media reports are not controlled.

The trade-offs to be kept in mind in designing regulatory mechanisms are between the cost of implementing and monitoring the regulatory systems that are intended to reduce harm, the value of the harm reduction, and the extent to which the regulations inhibit the appropriate medical uses they are supposed to permit, thus reducing benefits. How these trade-offs play out in practice will be reviewed briefly by way of analogy. Specifically, the regulation of the psychiatric practice of electroconvulsive therapy (ECT),¹³¹⁰ ¹³¹¹ the use of methadone and LAAM in the treatment of narcotic addiction,¹³¹² ¹³¹³ and the use of thalidomide in the treatment of erythema nodosum leprosum (ENL), a complication of leprosy,¹³¹⁴ ¹³¹⁵ will be explored for regulatory experiences that might be applicable to

¹³⁰⁶Benedict A, Saks M. The Regulation of Professional Behavior: Electroconvulsive Therapy in Massachusetts. *J Psychiat Law* (Summer 1987): 248.

¹³⁰⁷21 CFR 1300-1316 concern DEA regulations for the manufacture and use of controlled substances for medical and scientific purposes.

¹³⁰⁸Cooper J, Czechowicz D, Molinari S. (eds.) *Impact of Prescription Drug Diversion Control Systems on Medical Practice and Patient Care*. NIDA Research Monograph Series #131. Washington, DC, NIH Publication # 93-3507, 1992.

¹³⁰⁹21 CFR 202 Prescription Drug Advertising. For FDA’s most recent statement on direct-to-consumer advertising, see Guidance For Industry Consumer-Directed Broadcast Advertisements, August 1999. <http://www.fda.gov/cder/guidance/1804fnl.pdf> and <http://www.fda.gov/cder/guidance/1804q&a.htm>

¹³¹⁰NIH Consensus Statement. Electroconvulsive Therapy. *NIH Consensus Statement Online* 1985 Jun 10-12 [cited 2000, May 1]; 5(11):1-23.

¹³¹¹American Psychiatric Association Task Force on ECT. *The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training and Privileging*. Washington, DC. American Psychiatric Press, 1990.

¹³¹²NIH Consensus Statement. Effective Medical Treatment of Opiate Addiction. 15 (November 17-19, 1998) 6:1-38. National Institutes of Health. <http://odp.od.nih.gov/consensus/cons/mental.htm>

¹³¹³64 FR 39810 (July 22, 1999). Narcotic drugs in maintenance and detoxification treatment of narcotic dependence; repeal of current regulations and proposal to adopt new regulations.

¹³¹⁴Annas G, Elias S. Thalidomide and the Titanic: reconstructing the technological tragedies of the twentieth century. *Am J Pub Health* 89 (January 1999) 1:98-101.

psychedelic psychotherapy. The regulation of ECT is reviewed because it, along with psychedelic psychotherapy, is among the most controversial psychiatric practices of the last sixty years. The regulation of methadone in the treatment of addiction is reviewed because it is among the most highly regulated of all medical procedures, and because the treatment of drug abuse has been proposed as one application of psychedelic psychotherapy. The regulation of thalidomide is reviewed because the FDA has invoked unprecedented authority to impose a comprehensive set of controls on its medical use.¹³¹⁶

This chapter will concentrate on proposals for regulations that can be imposed and implemented by FDA. A thorough review of the regulatory authority granted by Congress to FDA and DEA will demonstrate that once a psychedelic drug is approved for one clinical indication, both FDA and DEA lack the authority to restrict its use for additional clinical indications.^{1317 1318 1319} This is true even if that psychedelic drug is placed in Schedule II, the most restrictive Schedule for prescription drugs. Since neither FDA nor DEA can limit the range of medical uses for a psychedelic drug once it is approved for medical use for one indication, the focus of FDA efforts to reduce misuse, abuse and diversion needs to be on controls over the practitioners who will be permitted to prescribe the psychedelic drug and on the settings in which this medical use will be permitted to take place. A proposal will be elaborated for a system of specially-licensed psychiatrists and psychotherapists working within clinical settings that must meet certain minimum standards. This chapter also proposes the distribution of psychedelics directly to physicians through the mail from one centralized production and distribution facility, as well as the establishment of a national registry of patients that will record information about all treatment sessions.¹³²⁰ These

¹³¹⁵For a complete overview, see FDA website at <http://www.fda.gov/cder/news/thalinfo/default.htm>

Thalidomide Information: FDA Announces Approval of Drug for Hansen's Disease (Leprosy) Side Effect; Imposes Unprecedented Authority to Restrict Distribution.

¹³¹⁶21 CFR 314.520 Approval with Restrictions to Assure Safe Use.

¹³¹⁷37 FR 16503 (August 15, 1972) Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration; Notice of Proposed Rule Making. "Once the new drug is in a local pharmacy after interstate shipment, the physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the Food and Drug Administration."

¹³¹⁸Christopher W. Off-Label Prescription: Filling the Regulatory Vacuum. *Food Drug Law J*48 (1993) 2:247-262.

¹³¹⁹Henry V. Off-label Prescribing. *J Leg Med*20 (1999): 365-383.

¹³²⁰A national registry of patients raises serious concerns about privacy. As will be discussed within this chapter, such a registry has already been required in patients receiving thalidomide and GHB. Exactly how the privacy rights of these patients are being balanced against regulatory needs to protect against misuse, abuse and diversion is still being determined. The best practices and compromises reached in these situations will guide the design of the patient registry for psychedelic psychotherapy. In the case of GHB, the

procedures have multiple benefits and will help minimize misuse, abuse and diversion.

The issue of limiting the effect of information/advertising about the medical use of psychedelic psychotherapy on the non-medical use of psychedelics will be reviewed in light of the difficulties in estimating what those effects might actually be. The issue will also be discussed in the context of FDA policies toward pharmaceutical advertising of approved drugs,¹³²¹ and the First Amendment freedom-of-speech issues that FDA has been wrestling with in its efforts to limit the dissemination of information on unapproved uses (those uses which do not appear on the FDA-approved labelling of the drug and are known as “off-label” uses) of approved drugs.¹³²² ¹³²³ A limited “voluntary” restriction on advertising to the general public will be proposed in the initial phase of the prescription availability of psychedelic psychotherapy.

The recommendations will be elaborated in some detail and then summarized in the concluding section.

FDA Authority to Impose Special Restrictions

The proposals that will be made for controlling the prescription use of a psychedelic drug as an adjunct to psychotherapy go well beyond the norm for drugs approved by FDA. This raises the question of whether FDA actually has the authority to impose the standards that will be recommended in this chapter. The current statutory authority, or lack thereof, will be discussed for the following policy options: potential restrictions on off-label uses, restricting the use of drugs to physicians with special training or registration (specialist-only approvals), limiting use to certain locations such as hospitals and other in-patient facilities or out-patient clinics, limiting the methods of distribution, and creating a national registry of patients with information about all treatment sessions. Each of these policy options contributes in varying degrees to the control and minimization of misuse, abuse and diversion. FDA authority to control advertising as a method of limiting the impact of the medical use of psychedelic psychotherapy on non-medical use patterns will also be reviewed.

FDA Authority to Limit Off-Label Prescription

Limitations on the authority of the FDA to regulate the practice of medicine appear in the Federal Food, Drug, and Cosmetic Act of 1938.¹³²⁴ The FDA’s jurisdiction to restrict pharmaceutical distribution company will keep the list, which will not be made available to the sponsor.

¹³²¹21 CFR 202 Prescription Drug Advertising.

¹³²²Washington Legal Foundation v. Henney. Civil Action 94-1306 (RCL) United District Court for the District of Columbia. 56 F. Supp. 2d 81; 1999 U.S. Dist. July 28, 1999, Decided.

¹³²³Murphy A. It’s Time to Make a Good Agency Better: The Food and Drug Administration Act of 1997 and the First Amendment. *Food Drug Law J* 53 (1998) 4:603-625.

¹³²⁴Hutt P. Regulation of the Practice of Medicine under the Pure Food and Drug Laws. Speech presented at

the purposes for which a physician may prescribe any approved drug was further limited as a result of *U.S. v. Phelps Dodge Mercantile Co.* in 1946.¹³²⁵

Phelps Dodge established that the FDA's authority to seize adulterated food was limited to instances where the food was adulterated when introduced into interstate commerce and did not extend to food that becomes adulterated afterwards. Phelps Dodge was interpreted to mean that FDA could not limit the use of a prescription drug after it was introduced into interstate commerce as long as the drug was neither adulterated¹³²⁶ nor misbranded¹³²⁷ when it was introduced into interstate commerce. This standard required that neither the shipper (most likely the manufacturer or agent of the manufacturer) nor the recipient (most likely a wholesale distributor or a pharmacy) intended that the drug be used for an indication that had not been approved by the FDA. Since it is the physician who determines the indication for which a prescription drug will be used, the criteria established by Phelps Dodge for manufacturers and pharmacists had no impact on physicians.

Two years after *U.S. v. Phelps Dodge Mercantile Co.*, Congress passed the Miller Amendment¹³²⁸ which extended the jurisdiction of the FDA to include drugs that become adulterated or misbranded after introduction into interstate commerce. Congress did not, however, specifically extend the jurisdiction of FDA to regulate the use of unapproved new drugs (i.e., without an approved NDA) after they have entered into interstate commerce. The Miller Amendment's silence regarding unapproved new drugs further supported the view that Congress did not intend for FDA to have such authority. In the Kefauver-Harris Amendments of 1962, Congress continued the policy of avoiding restrictions on the practice of medicine. Subsequent efforts by the FDA and its allies in Congress to expand FDA authority to control the off-label use of prescription drugs were unsuccessful.¹³²⁹

the 72nd Annual Conference of the Association of Food and Drug Officials of the United States, June 19, 1968. "The legislative history of the comprehensive Federal Food, Drug, and Cosmetic Act of 1938 is replete with statements that the statute was not intended to regulate the practice of medicine."

¹³²⁵Kessler D. *Regulating The Prescribing of Human Drugs for Non-approved Uses under the Food, Drug and Cosmetic Act*, 15 *Harv. J. Legis.* 693 (1978). Dr. Kessler indicated that, "Phelps Dodge shocked the FDA. The original 1906 Food and Drug Act had been interpreted to permit seizure for adulteration that occurred after interstate shipment."

¹³²⁶21 USC §351.

¹³²⁷21 USC §352.

¹³²⁸Miller Amendment of 1949, 80 P.L. 749; 80 Cong. Ch. 613; 62 Stat. 582. June 24, 1948. Chap. 613, § 2.

¹³²⁹The FDA has long wanted to obtain the authority to regulate some aspects of off-label uses but has been unable to do so. In a Notice of Proposed Rule Making, 37 Fed Reg 16,503 (August 15, 1972), the FDA proposed that it be able to take action when an unapproved use endangered patients or created a health hazard. The FDA wanted to be able to revise the package insert to contain a specific contraindication for an off-label use (as opposed to the current situation where the insert contains information related only to the

FDA's limited authority in controlling off-label uses was acknowledged in an article written by Dr. David Kessler and published in 1978, well before he was appointed FDA Commissioner in 1990.¹³³⁰ In the article, which focused on FDA authority to regulate the prescription of drugs for unapproved uses, Dr. Kessler proposed that FDA be given the power to disapprove certain uses of prescription drugs. Rather than prohibiting all off-label uses, Dr. Kessler argued that the power to disapprove certain uses would be a more limited use of FDA authority and would have the least impact on the practice of medicine.

Dr. Kessler noted that this proposal had some disadvantages related to the difficulty in choosing the appropriate standard of evidence needed to justify a decision to disapprove a particular use, and in the need to avoid undue interference with medical practice. Nevertheless, the major disadvantage noted by Dr. Kessler to this proposal was that it would require new legislation.¹³³¹

In 1981, the Fifth Circuit Court of Appeals rejected FDA's effort to prevent physicians from prescribing a drug off-label.¹³³² In 1983, the D.C. Circuit Court stated, "Congress would have created havoc in the practice of medicine had it required physicians to follow the expensive and time consuming procedures of obtaining FDA approval before putting drugs to new uses."¹³³³ That Dr. Kessler, an FDA Commissioner particularly adept at bureaucratic turf-building, was unable during his six years as Commissioner to extend formally the reach of the FDA regarding control over off-label uses of prescription drugs illustrates the strong resistance in the medical profession and in Congress to giving the FDA any such authority.

In the 1997 Food and Drug Administration Modernization Act, Congress explicitly reaffirmed its rejection of any FDA claim to regulate off-label uses of devices, stating, "[n]othing in this Act shall be construed to limit or interfere with the authority of the health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate healthcare practitioner-patient relationship."¹³³⁴ FDA regulations currently state that no prior permission is required of FDA "for the use in the practice of medicine for the unlabeled indication of a new drug product."¹³³⁵ As James Beck

approved indication, 21 USC 352 (f)), order a manufacturer to obtain and submit data concerning the unapproved use, and limit the distribution of the drug to physicians with special qualifications or to special channels such as hospital pharmacies, etc. Criticism from the American Medical Association and numerous physicians forced the FDA to back away from adopting a final version of its proposed rule, though it announced that it would do so in 40 Fed Reg 15,393 (April 7, 1975).

¹³³⁰Kessler (1978).

¹³³¹Ibid.,759. "Although total withdrawal is currently permitted, no provision in the FDCA specifically grants the necessary authority for disapproval."

¹³³²United States v. Evers, 643 F.2d 1043 (5th Cir. 1981).

¹³³³Chaney v. Heckler, 718 F.2d 1174, (D.C. Cir. 1983).

¹³³⁴Food and Drug Administration Modernization Act of 1997. 105 P.L. 115; § 214.

and Elizabeth Azari state, “FDA never has had the authority to regulate the practice of medicine; physicians may use legally marketed drugs or devices in any way that they believe, in their professional judgment, will best serve their patients. Courts have repeatedly recognized the propriety of off-label use.”¹³³⁶

Extent of Off-Label Prescribing

Much off-label prescribing is simply the use of a different dosage or dosage schedule for the same clinical condition for which the drug has been approved and labelled. However, a substantial amount of off-label use is indeed for entirely different indications. Though no precise statistics exist, it is estimated that roughly 40% - 60% of all prescriptions in the United States are for unapproved uses.¹³³⁷ A 1993 survey of 251 physicians revealed that 88% used drugs for unapproved purposes and 25% prescribed on a daily basis at least one drug for an off-label indication.¹³³⁸

There are several important public health benefits that accrue from the use of drugs for off-label indications. Most importantly, it cannot be assumed that every unapproved use is inappropriate and without medical benefit just because it has not been formally sanctioned by the FDA. One reason is that the standard of evidence for FDA approval of a drug, “substantial evidence” involving “adequate and well-controlled investigations,”¹³³⁹ is much higher than that required by a physician to justify a decision to prescribe a drug to a patient. Many millions of dollars must be spent on clinical trials and many years of testing and FDA review are required before a drug can become approved for a specific indication. On the other hand, anecdotal reports from just a few patients or medical hypotheses can point to important and even life-saving new treatments. The value of penicillin, for example, was discovered through just a few initial anecdotal reports. Nor were controlled experiments needed to discover some of the therapeutic benefits of aspirin, insulin, barbiturates or chloral hydrate.¹³⁴⁰

The process of determining exactly what goes on a drug label also supports the view that off-label uses cannot be assumed to be without medical benefit. The drug label represents a compromise between the drug sponsor and the FDA. The drug sponsor has financial incentives to get the drug to market as quickly as possible and may not want to

¹³³⁵21 CFR 312.2 (d). Unlabeled indication.

¹³³⁶Beck J, Azari E. FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions. *Food Drug Law J* 53 (1998) 1:76.

¹³³⁷Personal communication. Professor Michael Montagne, Dept.Pharm. Sci., Mass.College of Pharmacy, Boston, MA. January 21, 1997.

¹³³⁸Serradell J, Galle B. Prescribing for Unlabeled Indications. *HMO Pract.* 7 (March 1993) 1:44-7.

¹³³⁹21 USC §355 (1970).

¹³⁴⁰Lasagna L. Clinical Trials in the Natural Environment. in (eds.) Stiechele C, W. Abshagen W, Koch-Weser J. *Drugs Between Research and Regulation*. Darmstadt: Steinfopff Verlag, 1985: 45-49.

expend the funds or the time to develop scientific data on supplemental uses of the drug. In addition, one author noted that many of the warnings on labels may be “unsubstantiated, unexplained, and frivolous.”¹³⁴¹ These warnings may not be appropriate in certain individual cases, with the physician being in the best position to determine what drug in what amounts each unique patient should be prescribed.

There are risks associated with the prescription of drugs for unapproved uses. This is due primarily to that fact that the physician has far less information on which to base prescribing decisions for off-label indications as compared to the approved indication. The FDA can act in an educational capacity to prevent harm to public health through controls on labeling and public announcements. Other checks on improper prescribing are the tort law system of civil malpractice suits and state medical licensing boards which can review the behavior of physicians in the context of license renewals or disciplinary actions.¹³⁴²

One arguably counter-productive check on off-label prescriptions is that insurance companies sometimes balk at covering the use of drugs that are prescribed off-label. Veronica Henry, a pharmacist and lawyer, comments, “Many insurers and state programs, such as Medicaid, routinely deny reimbursement for drugs prescribed for off-label indications...The prevalence of off-label drug use in routine clinical practice argues for articulation of an explicit national reimbursement policy for off-label uses so that patients will receive the most medically appropriate therapy.”¹³⁴³

DEA Authority to Limit Off-Label Prescription

FDA shares authority with DEA in the regulation of the medical uses of controlled substances. Though FDA lacks authority to control off-label prescriptions, the Attorney General has a mandate to prevent the diversion to non-medical uses of controlled substances approved for prescription use. This authority includes the power to control a drug by placing it in one of five different schedules (each schedule imposes a specific set of control mechanisms on the diversion to non-medical uses of drugs in that schedule) and to transfer the drug between schedules, based on certain criteria and findings of fact.¹³⁴⁴ The Attorney General is given no specific authority to regulate the medical use of prescription drugs other than through the controls over drug diversion inherent in each schedule.

The Attorney General is also authorized “to promulgate rules and regulations and to charge reasonable fees relating to the registration and control of the manufacture, distribution and dispensing of controlled substances.”¹³⁴⁵ Physicians are specifically

¹³⁴¹Archer A. Guide into Chaos: Resist It. *JAMA* 227 (1974): 1397-98.

¹³⁴²Proposals have also been made to institute formal physician peer review mechanisms for prescribing off-label. Shapiro C. Limiting Physician Freedom to Prescribe a Drug for any Purpose: The Need for FDA Regulation, 73 *Nw L Rev* 801 (1979): 849.

¹³⁴³Henry (1999): 378.

¹³⁴⁴Controlled Substances Act of 1970. 91 P.L. 513; Part B. Authority to Control; Standards and Schedules. Authority and Criteria for Classification of Substances.

required to register in order to obtain a permit to prescribe controlled substances. Physicians can be denied a registration for certain factors related to the protection of the public interest and public health and safety. None of these factors speaks directly to prescribing a controlled drug for an off-label indication or implies that such conduct is inappropriate.¹³⁴⁶

A physician's registration can be revoked for certain enumerated factors such as lying on the application, being convicted of a felony related to a controlled substance, or having his or her State license or registration revoked, suspended or denied. A physician's registration can also be revoked if "[the doctor] has committed such acts as would render his registration under section 823 of this title inconsistent with the public interest as determined under such section."¹³⁴⁷ The public interest is defined as the same conditions required for registration. The only potentially applicable condition is "5) such other factors as may be relevant to and consistent with the public health and safety."¹³⁴⁸

¹³⁴⁵Part C. Registration of Manufacturers, Distributors and Dispensers of Controlled Substances. Sec. 301. Rules and Regulations.

¹³⁴⁶Dangerous Drug Diversion Control Amendment. 98 P.L. 473; 98 Stat. 2070, October 12, 1984. Part B, Sec. 511. 21 USC 823 (f). These factors [for evaluating the licensing of physicians to prescribe controlled substances] include 1) the recommendation of the appropriate State licensing board or professional disciplinary authority; (2) the applicant's experience in dispensing, or conducting research with respect to controlled substances, (3) The applicant's conviction record under Federal or State laws relating to the manufacture, distribution, or dispensing of controlled substances; 4) Compliance with applicable State, Federal or local laws relating to controlled substances; and 5) such other conduct which may threaten the public health and safety."

¹³⁴⁷21 USC 824 (a) (4).

¹³⁴⁸62 FR 6164 (February 11, 1997). Office of National Drug Control Policy, Administration Response to Arizona Proposition 200 and California Proposition 215. DEA cited potential violations of the public interest in its threats to revoke the registration of physicians who recommend or approve the use of smoked marijuana in California, as they are authorized to do under Proposition 215, or of physicians in Arizona who prescribe marijuana, as they are authorized to do under Proposition 200 (even though there is no source for marijuana by prescription). The position of the Department of Justice is presented in a document released on December 30, 1996 by Gen. Barry McCaffrey, Director of the Office of National Drug Control Policy, entitled "The Administration's Response to the Passage of California Proposition 215 and Arizona Proposition 200." According to the document, "a practitioner's action of recommending or prescribing Schedule I controlled substances is not consistent with the "public interest" (as that phrase is used in the federal Controlled Substances Act) and will lead to administrative action by the DEA to revoke the practitioner's registration." Attorney General Reno's threat to revoke physicians' licenses is predicated on the fact that marijuana is still in Schedule I and cannot be legally prescribed for any purpose. This is a fundamentally different situation than a physician prescribing a Schedule 2 drug for an off-label indication. However, the furor over Proposition 215 is in part a reaction to a clause that permits physicians to recommend or approve marijuana for a list of clinical indications or "any other illness for which marijuana

Given that Congress never indicated that prescribing off-label is a danger to the public health and safety, even with Schedule II drugs, it would appear that DEA lacks the jurisdiction categorically to prohibit the off-label prescription of controlled substances. Other than methadone, which is a unique situation discussed below, DEA has refrained from attempting to prohibit off-label uses of Schedule II drugs until October 1985, when it unsuccessfully tried to restrict the off-label use of Marinol, a capsule that contained a synthetic version of THC, the main active ingredient in marijuana. It has not attempted such restrictions since.

The Case of the THC Capsule

Four months after the FDA approved Marinol for prescription use, the DEA announced its effort to restrict the freedom of physicians to prescribe Marinol for any off-label uses. Through the publication in the Federal Register of a “Notice of proposed rulemaking”¹³⁴⁹ signed by Mr. Gene Haislip, DEA Deputy Assistant Administrator, Office of Diversion Control, DEA attempted to impose a level of restriction for Marinol that did not exist for any other prescription drug, including methadone¹³⁵⁰ or cocaine.¹³⁵¹ DEA provides relief.” The “any other illness” language carries the same meaning as the right to prescribe a drug for any off-label indication.

A successful class action suit was filed on January 14, 1997 in the United States District Court Northern District of California against Gen. Barry McCaffrey, Attorney General Janet Reno, DEA Administrator Thomas Constantine, and Donna Shalala, Secretary of HHS. The suit cites First Amendment freedom-of-speech protection from any revocation of physician’s registrations and asked for an injunction against the revocation of any physician’s license on the basis of the threats in the December 30, 1996 position paper. See: Wells D. Casenote: Conant V. McCaffrey: Physicians, Marijuana, and the First Amendment. 70 *U Colo L Rev* 975 (Summer 1999).

¹³⁴⁹Changes in Protocol Requirements for Researchers and Prescription Requirements for Practitioners. DEA. 50 FR 42184 (October 18, 1985).

¹³⁵⁰Methadone is approved for relief of severe pain, detoxification treatment of narcotic addiction, and temporary maintenance treatment of narcotic addiction. The off-label use of methadone for other indications is not prohibited, though any such use would attract the attention of drug enforcement officials. The off-label use of methadone for the treatment of narcotic addiction (i.e. the administration of doses in excess of those approved for listing in the physician package insert) is prohibited by regulation based on statutory authority to be discussed later in this chapter. There can be no dosage-related off-label use of methadone for severe pain, since there are no specific dosage limits for the use of methadone for severe pain. The label states, “dosage should be adjusted according to the severity of the pain and the response of the patient. Occasionally, it may be necessary to exceed the usual dosage recommended in cases of exceptionally severe chronic pain or in those patients who have become tolerant to the analgesic effect of narcotics.” PDR (1998): 2549.

¹³⁵¹Cocaine is approved for “the introduction of local (topical) anesthesia of accessible mucous membranes of the oral, laryngeal and nasal cavities.” PDR (1998): 541. There are no prohibitions on off-label uses.

announced its view that any off-label use of Marinol would be considered diversion that would subject the physician to revocation of DEA registration to prescribe controlled substances and “other criminal and civil sanctions provided by law.”¹³⁵² Since off-label use encompasses the use in the approved clinical indication of doses and dosing schedules that differ from those specified in the label, DEA’s effort to restrict the off-label use of Marinol “could negatively affect medical practice in the care of cancer patients”¹³⁵³ as well as limit potentially beneficial uses of Marinol for other clinical indications.

DEA cited U.S. treaty obligations under the Convention on Psychotropic Substances 1971¹³⁵⁴ and the requirements of the Controlled Substances Act of 1970, as amended by the Psychotropic Substances Act of 1978,¹³⁵⁵ as justification for this extraordinary action. The reliance on international treaty obligations was the best rationale that DEA could offer, since U.S. law contains no specific authority for DEA or FDA to prohibit the off-label use of any prescription drug, regardless of the abuse potential of the drug.

DEA based its authority on Article 7 of the Convention on Psychotropic Substances¹³⁵⁶ which specified the manner in which signatory nations are to control Schedule I drugs. The relevant section of Article 7 requires that parties to the Convention “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 Governments or specifically approved by them.”¹³⁵⁷ DEA put its emphasis

¹³⁵²50 FR 42184 (October 18, 1985).

¹³⁵³Joranson D, Gilson A. *Controlled Substances, Medical Practice and the Law.* in Schwartz H. (ed.) *Psychiatric Practice Under Fire- The Influence of Government, the Media, and Special Interests on Somatic Therapies.* Washington, DC: American Psychiatric Association Press, 1994: 179.

¹³⁵⁴The Convention on Psychotropic Substances (UN Treaty Series. Vol. 1019) was concluded at 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 (UN Treaty Series Vol. 520, US Treaties and other International Agreements. Vol 18 Part 2, 1967:1407), which concluded on March 30, 1961.

¹³⁵⁵Psychotropic Substances Act of 1978. 95 P.L. 633; 92 Stat. 3768. November 10, 1978. The Convention on Psychotropic Substances was not self-executing and needed to be enacted into U.S. law to take effect domestically. The Psychotropic Substances Act of 1978 was written to “enable the United States to meet all of its obligations under the Convention.”

¹³⁵⁶US Treaties and other International Agreements. Vol 32 Part 1, 1979-80. Convention on Psychotropic Substances: 553.

¹³⁵⁷The other requirements under Article 7 are that Parties shall “b) require that manufacture, trade, distribution and possession be under a special license or prior authorization; c) provide for close supervision of the activities and acts mentioned in paragraphs (a) and (b); d) restrict the amount supplied to a duly authorized person to the quantity required for his authorized purpose; e) require that persons performing

on the “very limited medical purposes” requirement.

Section (a) and the remaining sections of Article 7 do indeed enable the DEA and the FDA to limit the use of Schedule I drugs to such uses as specifically described in a scientific protocol subject to pre-approval by the FDA. The use of any Schedule I drug outside of the parameters of an approved protocol is indeed forbidden.

The argument put forth by the DEA overlooked the crucial fact that Article 7 applies only to Schedule I drugs.¹³⁵⁸ The approval of Marinol for marketing by the FDA effectively redefined it as a Schedule II drug.¹³⁵⁹ Furthermore, DEA itself had proposed that Marinol be transferred from Schedule I to II.¹³⁶⁰ DEA tried to obfuscate the restricted applicability of Article 7 by noting that at the time of the Notice of Proposed Rulemaking, Marinol was still nominally a Schedule I drug in the United States. DEA claimed that even though the FDA had already determined that it no longer fit the definition of a Schedule I drug, it remained a Schedule I drug internationally according to the Convention.

Article 9 of the Convention addresses the issue of controls on the prescription of Schedule II drugs.¹³⁶¹ No restrictions on the off-label prescription of Schedule II drugs

medical or scientific functions keep records concerning the acquisition of the substances and the details of their use, such records to be preserved for at least two-years after the last use recorded therein; and f) prohibit export and import except when both the exporter and importer are the competent authorities or agencies of the exporting and importing country or region, respectively, or other persons or enterprises which are specifically authorized by the competent authorities of their country or region for the purpose. The requirements of paragraph 1 of article 12 for export and import authorizations for substances in Schedule II shall also apply to substances in Schedule I.”

¹³⁵⁸An argument could be made that since THC was still in Schedule I internationally, therefore United States treaty obligations still required it to keep THC in Schedule I domestically. However, Sec. 101 3 (c) of the Psychotropic Substances Act of 1978, which formally adopted the Convention on Psychotropic Substances, states, “Nothing in the Convention will interfere with ethical medical practice in this country as determined by the Secretary of Health, Education, and Welfare on the basis of a consensus of the views of the American medical and scientific community.” FDA approval of a drug for marketing is indicative of a consensus of the views of the American medical and scientific community. Therefore, controls over Schedule I drugs required under Article 7 of the Convention do not apply when FDA has approved the medical use of a drug.

¹³⁵⁹FDA approval for marketing means that the drug in question does have a currently accepted medical use and currently accepted safety for use under medical supervision.

¹³⁶⁰50 Fed Reg 42186 (October 18, 1985).

¹³⁶¹Article 9, Prescriptions. 1) The Parties shall require that substances in Schedule II, III, and IV be supplied or dispensed for use by individuals pursuant to medical prescription only, except when individuals may lawfully obtain, use, dispense or administer such substances in the duly authorized exercise of therapeutic or scientific functions. 2) The Parties shall take measures to ensure that prescriptions for substances in Schedules II, III, IV and issued in accordance with sound medical practice and subject to such

were mentioned. Article 9 requires only that Schedule II drugs be prescribed “in accordance with sound medical practice” and be subject to regulation that “will protect the public health and welfare.”

The Attorney General is charged with ensuring that the United States fulfills its obligations under international treaty responsibilities.¹³⁶² However, the Psychotropic Substances Act of 1978, which executed US obligations under the Convention on Psychotropic Substances, contains an unambiguous rejection of the argument that the US could be forced to place extraordinary controls on the medical use of prescription drugs as a result of treaty obligations. The Act explicitly states, “nothing in the Convention will interfere with ethical medical practice as determined by the Secretary of Health, Education and Welfare [now HHS] on the basis of a consensus of the view of the American medical and scientific community.”¹³⁶³ DEA made no attempt in its Notice of Proposed Rulemaking to explain why it could impose special restrictions on the ability of physicians to prescribe Marinol for off-label uses when such restrictions ran counter to policies about off-label prescriptions that were supported by the Secretary of HHS and held by a consensus of the regulation, particularly as to the number of times they may be refilled and the duration of their validity, as will protect the public health and welfare. 3) Notwithstanding paragraph 1, a Party may, if in its opinion local circumstances so require and under such conditions, including record-keeping, as it may prescribe, authorize licensed pharmacists or other licensed retail distributors designated by the authorities responsible for public health in its country or part thereof to supply, at their discretion and without prescription, for use for medical purposes by individuals in exceptional cases, small quantities, within limits to be defined by the Parties, of substances in Schedules III and IV.

¹³⁶²Controlled Substances Act of 1970. 91 P.L. 513; Part B, Sec. 201 (d) “If control is required by United States obligations under international treaties, conventions, or protocols in effect on the effective date of this part, the Attorney General shall issue an order controlling such drug under the schedule he deems most appropriate to carry out such obligations, without regard to the findings required by subsection (a) of this section or section 202 (b) and without regard to the procedures prescribed by subsections (a) and (b) of this section.” This language is intended to permit the Attorney General to rapidly schedule a drug without going through formal proceedings.

¹³⁶³Psychotropic Substances Act of 1978. 95 P.L. 633, Sec. 101 (3) (C). Sec. 101 further states that the implementation of the Convention shall be “within the framework of the procedures and criteria for classification of substances provided in the Comprehensive Drug Abuse Prevention and Control Act of 1970. This will ensure that (A) the availability of psychotropic substances to manufacturers, distributors, dispensers, and researchers for useful and legitimate medical and scientific purposes will not be unduly restricted; (B) nothing in the Convention will interfere with bona fide research activities;” Explicit limits were also placed on the potential impact of the Convention on bona fide research with Schedule I drugs in Dangerous Drug Diversion Control Amendments. 98 P.L. 473, Part B Sec. 511, “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.”

American medical and scientific community. In its proposed rulemaking, DEA acknowledged that Marinol might have other legitimate applications outside of its approved use. DEA therefore proposed that any off-label use be regulated in the same manner as research with a Schedule I drug, with protocols submitted to FDA and Institutional Review Boards (IRB) for pre-approval. DEA must certainly have been aware that the substantial amounts of time and resources that are required to obtain permission for and conduct FDA-approved clinical research would place the use of Marinol for off-label indications beyond the reach of virtually all individual physicians.

Response to DEA Proposed Controls on Marinol

Not surprisingly, DEA's attempt to impose extraordinary and precedent-setting controls on the prescription of Marinol was met with opposition by the American Medical Association (AMA) and the American Pharmaceutical Association (APhA), among others. AMA submitted a comment to DEA that it "vigorously" opposed "restricting the therapeutic use of dronabinol [Marinol] (or any other FDA-approved drug) to the approved indications."¹³⁶⁴ AMA argued that labeling of a drug is intended to advise but not restrict the physician and that the very narrow labeling of Marinol proposed by DEA would have the seemingly unintended effect of restricting its use as an antiemetic even for cancer patients who received radiation therapy instead of chemotherapy. AMA further argued that diversion of Marinol during its period of research had not been a problem, that other mechanisms existed to control the diversion of Schedule II drugs, that the problems associated with the diversion of cocaine and various opiates in Schedule II were greater than that with Marinol yet no extraordinary controls were imposed on those drugs, and that physicians would be needlessly subjected to criminal prosecution for practicing medicine as they saw fit.¹³⁶⁵ The American Pharmaceutical Association noted that the DEA's proposed regulation was unprecedented and that it would impose an undue risk of criminal prosecution on pharmacists.¹³⁶⁶

On January 14, 1986, almost two months after the comments of the AMA, APhA and others had been received, DEA Diversion Control Deputy Director Ronald Buzzeo spoke at the annual meeting of the National Association of Pharmaceutical Manufacturers. He used the opportunity to threaten to wield the DEA's power to block the proposed rescheduling of Marinol if agreement could not be reached on the imposition of restrictions on all off-label indications.¹³⁶⁷

¹³⁶⁴Staff. F-D-C Reports. (February 3, 1986): 5-6.

¹³⁶⁵For a general statement of AMA policy in regard to the use of approved drugs for unlabeled indications, see; Cranston J, Williams M, Nielsen N, Bezman R. Report of the Council on Scientific Affairs: Unlabeled Indications of Food and Drug Administration-Approved Drugs. *Drug Info J.* 32 (1998) 4: 1049-1061.

¹³⁶⁶Staff. F-D-C Reports. (February 3, 1986): 5-6.

On May 13, 1986, almost four months after Mr. Buzzeo's speech, DEA capitulated. It announced in the Federal Register that it was withdrawing its proposed rule because the Administrator, "having considered the requirements of the Controlled Substances Act and the Convention on Psychotropic Substances and taking into account the comments and objections, has decided to proceed with the rescheduling of the dronabinol product [Marinol]."1368

In a separate Federal Register announcement on the same day, DEA issued a final rule and statement of policy.¹³⁶⁹ In its final rule, DEA formally rescheduled Marinol from Schedule I to Schedule II and imposed the standard system of controls for any Schedule II drug without adding the proposed restrictions on off-label prescriptions.¹³⁷⁰ DEA noted that thirteen individuals or organizations had submitted comments responding to its proposal and that two of the thirteen had requested an administrative hearing.¹³⁷¹

DEA restated its opposition to the prescribing of Marinol off-label in the form of a non-binding Statement of Policy. This statement of policy noted that Marinol remained in Schedule I in the Convention of Psychotropic Substances¹³⁷² and that "prescribing which

¹³⁶⁷Staff. F-D-C Reports. (February 3, 1986): 5-6.

¹³⁶⁸51 FR 17494 (May 13, 1986). Withdrawal of Proposal to Change Protocol Requirements for Researchers and Prescription Requirements for Practitioners. DEA.

¹³⁶⁹51 Fed Reg 17476. (May 13, 1986). Rescheduling of Synthetic Dronabinol in Sesame Oil and Encapsulated in Soft Gelatin Capsules From Schedule I to Schedule II; Statement of Policy.

¹³⁷⁰Ibid. These controls include requirements for registration of anyone who manufactures, distributes, delivers, imports or exports Marinol, and procedures governing security, labelling and packaging, production quotas, inventory controls, record keeping, reports, order forms, prescriptions, importation and exportation, and criminal liability for inappropriate use.

¹³⁷¹The organizations that requested a hearing were the National Organization for the Reform of Marijuana Laws (NORML) and the Cannabis Corporation of America. Also commenting were the American College of Neuropsychopharmacology, Arkansas Department of Public Health, Committee on Problems of Drug Dependence, the Pharmaceutical Manufacturers Association, and others.

¹³⁷²Marinol was eventually placed in Schedule II internationally, but only after a long and rocky road. In 1987, the United States Attorney General petitioned the Convention to transfer Marinol from Schedule I to II. In 1989, the WHO Expert Committee reviewed the new data concerning the medical use of Marinol and recommended that the rescheduling petition be approved. The UN Commission on Narcotic Drugs (CND) rejected the recommendation and requested that the WHO Expert Committee re-evaluate the scientific data. In 1990, the Expert Committee completed its review of the latest data and recommended once again that Marinol be placed in Schedule II. On May 24, 1991, the United Nations Economic and Social Council (ESCOR) rescheduled delta-9-tetrahydrocannabinol from Schedule I to Schedule II of the 1971 Convention on Psychotropic Substances.

As an aside, one section of the Expert Committee's 1990 report is of particular relevance to the current debate in the United States about whether the acceptance of the medical use of marijuana will "send the wrong message" and lead to an increase in the non-medical use of marijuana, especially by young

deviates from the recognized approved medical use must be questioned in keeping with the United States obligations to prohibit all use except for scientific and very limited medical purposes.” DEA noted that any physician who prescribed Marinol for off-label uses “may subject his or her controlled substances registration to review under the provisions of 21 U.S.C. 823 (f) and 824 (a) (4) as being inconsistent with the public interest.” The Statement of Policy asserted that DEA will take action “if it is found that such distribution or dispensing constitutes a threat to the public health and safety.”¹³⁷³

In support of its statement of policy, DEA cited a Supreme Court case, *US v. Moore*.¹³⁷⁴ The legal issue in the case concerned the appropriate statutory basis for the prosecution of a physician for diversion. An evaluation of the factual basis of the case reveals a complete absence of justification for establishing DEA authority to prohibit all, or even any, off-label uses of Marinol or other controlled drugs.

Dr. Moore had operated a methadone prescription mill. In a five and a half month period between late August 1971 and early February 1972, Dr. Moore had prescribed over 800,000 methadone tablets and taken in at least \$260,000. Furthermore, Dr. Moore conducted few physical exams, ordered few tests, ignored the results of those tests he did order, based his fee on the number of tablets prescribed rather than on services rendered, kept few records, provided no follow-up or counseling, and operated even after the revocation of his FDA license to administer methadone maintenance, a license that was required at the time. Dr. Moore’s case is one of diversion for non-medical purposes. As such, it is not relevant to the situation of physicians who prescribe Marinol off-label for indications for which a reasonable argument can be made that the prescriptions are medically justified.

In a related case, an appellate court held that a physician needed only to have a “good faith” belief that an off-label prescription was being administered for a legitimate medical purpose.¹³⁷⁵ Clearly, off-label prescription does not equal diversion. DEA’s statement of policy comes down to an unjustified threat to do that which falls outside its jurisdiction: control off-label uses of scheduled drugs.

The lack of teeth in DEA’s statement of policy regarding the off-label prescription of Marinol was further evidenced in November 1992 in a letter from Dr. Jack Chow, Deputy Assistant Secretary for Public Health Policy, Office of the Assistant Secretary of Health, to people. The Committee considered the possibility that “the official recognition of the therapeutic usefulness of dronabinol might encourage the ‘medicinal’ use of cannabis and thus its abuse. However, cannabis is already the most widely abused illicit drug in the world, with an annual seizure figure of 30,000 to 40,000 tons. It is unlikely that such recognition will make a significant difference to the current level of massive cannabis abuse.”

¹³⁷³51 Fed Reg 17476. (May 13,1986).

¹³⁷⁴*United States v. Moore*, 423 U.S.122 (1975).

¹³⁷⁵*United States v. Rosenberg*, 515 F. 2nd 190 (9th Cir. 1975).

Dale Gieringer, Ph.D., Coordinator of California NORML, a marijuana legalization advocacy group. Dr. Gieringer had requested that Dr. James Mason, Assistant Secretary of Health, explain his assertion that Marinol was a legal substitute for smoked marijuana for a variety of clinical indications in the light of DEA's Statement of Policy regarding possible prosecution of physicians who prescribed Marinol off-label.¹³⁷⁶ According to Dr. Chow, "as a matter of policy, DEA will not [emphasis in original] revoke a registration or take criminal action against a physician who prescribes Marinol for medical indications other than nausea associated with cancer chemotherapy as long as the medication serves a direct, legitimate purpose in a patient's care."¹³⁷⁷

A likely indication of the standards which the DEA can use to evaluate whether the prescription of Marinol "serves a direct, legitimate purpose in a patient's care" can be determined by reviewing the standards that the Department of Justice announced it will use to determine if smoked marijuana or any other Schedule I drug is being appropriately recommended, approved or prescribed by physicians in California and Arizona pursuant to voter initiatives passed in 1996.¹³⁷⁸ These standards do not focus on what constitutes good

¹³⁷⁶Dale Gieringer had requested a clarification of a June 4, 1992 letter from Dr. James Mason, Assistant Secretary of Health, to Mr. Dennis Peron explaining a policy decision to close to new applicants a program to provide legal supplies of marijuana to patients approved by the FDA for participation in the Compassionate IND program. The rationale for closing the program was based on the arguments that the program did not generate scientific data but just provided marijuana on a compassionate basis and that an alternative drug, Marinol, was legally available for use as an alternative to marijuana for such uses as the treatment of AIDS wasting. Though Marinol is currently approved by the FDA for the treatment of AIDS wasting, it was not so approved at the time of Dr. Mason's closure of the single patient IND program.

¹³⁷⁷Chow J. Deputy Assistant Secretary for Public Health Policy, Office of the Assistant Secretary of Health, HHS. Letter to Dale Gieringer, Coordinator of California NORML. November 30, 1992. Dr. Chow replied, "The DEA policy statement published in the Federal Register on May 13, 1986, (51 Fed Reg. 1746 [sic]) states that the DEA may [emphasis in original] revoke registrations or criminally prosecute physicians who prescribe Marinol for medical indications outside the approved use associated with cancer treatment, if such prescription is inconsistent with the public interest. My staff have had several discussions with DEA on this issue, however, and we have been assured that as a matter of policy, DEA will not [emphasis in original] revoke a registration or take criminal action against a physician who prescribes Marinol for medical indications other than nausea associated with cancer chemotherapy as long as the medication serves a direct, legitimate purpose in a patient's care. It should be noted that DEA has never taken adverse action against any physician for prescribing "off-label" use of Marinol. Physicians who appropriately prescribe Marinol for medical purposes other than cancer chemotherapy should not be affected."

¹³⁷⁸The position of the Department of Justice is presented in a document released on December 30, 1996 by Gen. Barry McCaffrey, Director of the Office of National Drug Control Policy, entitled "The Administration's Response to the Passage of California Proposition 215 and Arizona Proposition 200." <http://www.ncjrs.org/txtfiles/215rel.txt>

medical practice, but rather enumerate what kinds of evidence may be used to justify investigation and possible prosecution of a physician for inappropriately recommending, approving or prescribing marijuana or other Schedule I drugs. The factors include, “a) the absence of a bona fide doctor-patient relationship; b) a high volume of prescriptions or recommendations for a Schedule I drug; c) the accumulation of significant profits or assets from the prescription or recommendation of Schedule I controlled substances; d) Schedule I controlled substances being provided to minors; e) special circumstances, such as when death or serious bodily injury results from drugged driving.” The evaluation of the inappropriateness of all Schedule II prescriptions is likely to use these same or similar criteria, perhaps with the exception of the use of such medicines in minors. These criteria clearly do not categorically preclude off-label prescriptions of Schedule II drugs.

DEA Rescheduling of Marinol

As of July 2, 1999, the DEA, in cooperation with the FDA, formally reclassified Marinol from a Schedule II drug to a Schedule III drug.¹³⁷⁹ States are now free to do the same if they choose to do so. While DEA’s decision was perhaps motivated in part to enhance the medical use of Marinol as an alternative to smoked marijuana, the abuse potential of Marinol was found, in actual practice, to be minimal.¹³⁸⁰ The practical implications of the rescheduling are that in states that also reschedule Marinol to Schedule III, physician-written prescriptions will no longer be required and physicians will be permitted to phone a prescription into the pharmacy for a patient. Physicians can prescribe refills with the initial prescription so that it can be up to five months before another prescription would be required. From the point of view of off-label prescriptions, the rescheduling means that triplicate prescription programs for Schedule II drugs, in which the DEA is notified of every prescription, are no longer required in those states that have these programs. In those states that do reschedule Marinol to Schedule III, DEA will have no reporting mechanism capable of directly determining whether or not off-label prescriptions are even taking place.

¹³⁷⁹64 FR 35928 (July 2, 1999) Schedules of Controlled Substances: Rescheduling of the Food and Drug Administration Approved Product Containing Synthetic Dronabinol in Sesame Oil Encapsulated in Soft Gelatin Capsule from Schedule II to Schedule III.

¹³⁸⁰Calhoun S, Galloway G, Smith D. Abuse Potential of Dronabinol (Marinol). *J Psychoact Drug*30 (1998) 2:187-196. The authors report, “ Cannabis-dependent populations, such as those treated in our Clinic and seen by the addiction medicine specialists we interviewed, have demonstrated no interest in abuse of dronabinol. There is no street market for dronabinol, and no evidence of any diversion of dronabinol for sale as a street drug. Furthermore, dronabinol does not provide effects that are considered desirable in a drug of abuse. The onset of action is slow and gradual, it is at most only weakly reinforcing, and the overwhelming majority of reports of users indicate that its effects are dysphoric and unappealing. This profile of effects gives dronabinol a very low abuse potential.”

DEA Quotas

DEA does have one blunt regulatory instrument it can use to try to limit the total number of off-label prescriptions of controlled substances. DEA has been given the responsibility by the Controlled Substances Act,¹³⁸¹ and as a result of U.S. international treaty obligations,¹³⁸² to set annual quotas on the amount of controlled substances that are produced each year for “medical, scientific, research and industrial needs of the United States, for lawful export requirements, and for the establishment and maintenance of reserve stocks.”¹³⁸³ DEA, with input from FDA, can initially estimate the quota for the medical need for a psychedelic drug that is approved for prescription use on the basis of the indication for which it has been approved, thereby seeking to limit off-label uses on a macro-level. However, since off-label prescriptions are a legitimate medical use, DEA cannot prevent off-label prescriptions at the microlevel. If the demand by physicians for the psychedelic drug that had been approved for prescription were to exceed the available supply established under DEA quota, DEA could not refuse to increase the quota for the subsequent year on the grounds that some portion of the supply was being prescribed off-label. To prevent increasing the quota, DEA would need to establish that supplies were being diverted to non-medical uses, a factor independent of off-label prescription. To avoid an absence of supply between the time one year’s production quotas are completely distributed and DEA approval for an increased production quota, sponsors can request increases mid-year and do not need to wait until the end of the year.

DEA’s limited ability to use the quota system to control off-label prescription can be seen in a historical example that set the standards for DEA’s setting of quotas. In October 1985, DEA tried to control the diversion of Ritalin by setting a production quota for 1986 that was well below the medical need.¹³⁸⁴ Two pharmaceutical companies, Ciba-Geigy Corp. and MD Pharmaceutical, Inc., filed formal objections within the allotted 30-day period and requested a hearing before a DEA Administrative Law Judge.¹³⁸⁵ In March 1986, DEA

¹³⁸¹21 U.S.C. 826 § 306, 21 CFR 1303 Quotas.

¹³⁸²Articles 12, 19-21 of the Single Convention on Narcotic Drugs, Article 16 of the Convention on Psychotropic Substances.

¹³⁸³21 CFR 1303.11 Aggregate production quotas.

¹³⁸⁴Joranson, Gilson (1994):178. The initial quotas were proposed in 50 FR 40070 (October 1, 1985) Controlled Substances; Proposed Aggregate Production Quotas for 1986.

¹³⁸⁵“In a letter dated October 29, 1985, MD Pharmaceutical, Inc. (MD) submitted comments and objections and requested a hearing in the matter of the proposed 1986 aggregate production quota for methylphenidate. In a letter dated October 30, 1985, Ciba-Geigy Corporation (Ciba-Geigy) did the same.” 53 FR 50591 (December 16, 1988). Ciba-Geigy Corp. and MD Pharmaceutical, Inc.; 1986 Aggregate Production Quota, 1986 Individual Manufacturing Quotas, and 1986 Disposal Allocations for Methylphenidate. Final Rule by DEA Administrator John Lawn.

increased the quota, then increased it again in May 1986 but still refrained from granting a hearing.¹³⁸⁶ In June 1986, MD Pharmaceutical, Inc. again requested a hearing while Ciba-Geigy requested a hearing and also filed a petition before the U.S. Court of Appeals for the District of Columbia Circuit seeking review of DEA's actions.¹³⁸⁷ In July 1986, the DEA Administrator formally instructed the DEA Administrative Law Judge to proceed with a hearing,¹³⁸⁸ and DEA increased the quota once again.¹³⁸⁹

The outcome of the hearing was an order for DEA to increase the quota yet again.¹³⁹⁰ More importantly, the DEA Administrator reaffirmed the principle that, "The CSA requirement for a determination of legitimate medical need is based on the undisputed proposition that patients and pharmacies should be able to obtain sufficient quantities of methylphenidate, or of any Schedule II drug, to fill prescriptions. A therapeutic drug should be available to patients when they need it. To accomplish this a smooth flow of distribution is required. If there were periods during the year where there were shortages and patients were not able, because of the quotas, to obtain sufficient methylphenidate to fill their prescriptions, then the quotas would not be providing for the legitimate medical need in the United States."¹³⁹¹

The key factor in setting DEA quotas is whether there are sufficient supplies to enable all prescriptions to be filled. Since prescriptions can legitimately be written for both labeled and off-labeled indications, DEA's quota system cannot function as an effective method of controlling off-label use of controlled substances.

State Rescheduling of Controlled Substances to Permit Medical Uses

As mentioned above, the pharmaceutical company that markets Marinol needs to implement DEA's federal rescheduling of Marinol from Schedule II to Schedule III on a state by state basis, in order to enable physicians and patients to take advantage of the more relaxed regulations under Schedule III. Similarly, if FDA approves the medical use of

¹³⁸⁶Ibid.

¹³⁸⁷Ibid.

¹³⁸⁸Ibid.

¹³⁸⁹The quota was increased in 51 FR 24590 (July 7, 1986). Controlled Substances; Proposed Revised 1986 Aggregate Production Quotas.

¹³⁹⁰53 FR 50591. (December 16, 1988) Order, "The Administrator hereby orders that the DEA staff redetermine the 1986 aggregate production quota for methylphenidate so as to provide for the medical, scientific, research, and industrial needs of the United States, for lawful export requirements, and for the establishment and maintenance of reserve stocks. It is further directed that pursuant to the agreement entered into by DEA with the parties to the 1986 hearing conducted before the Administrative Law Judge, any increase in the 1986 aggregate production quota or to any individual quota shall not be offset by a lowering of any relevant quota for the year in which the adjustment is made."

¹³⁹¹Ibid., Paragraphs 19 and 20.

psychedelic psychotherapy and moves a psychedelic drug from the federal Schedule I to Schedule II, States still must decide whether or not to reschedule that psychedelic drug from Schedule I to Schedule II to permit its medical use in that state. An example of this process is the medical use of methadone. The use of methadone as a maintenance treatment for heroin addiction was first proposed in 1963¹³⁹² and its federal regulatory structure was established by the Controlled Substances Act of 1970. On May 1, 2000, fully thirty years after the Controlled Substances Act, the Vermont House of Representatives approved the use of methadone to treat narcotic addicts,¹³⁹³ making it the 43rd state to approve the use of methadone.¹³⁹⁴ Seven states still do not permit the use of methadone to treat narcotic addiction.¹³⁹⁵

Another illustrative example is LAAM, the long-lasting methadone that NIDA worked to develop for about twenty years and for which Pilot Drug invested substantial staff time in proactive protocol design and data analysis.¹³⁹⁶ Approved by the FDA in 1993, after 30 months, “LAAM has still not been approved in many of the states with the greatest number of narcotic treatment programs (e.g. New York, California, Illinois, Pennsylvania, Florida, New Jersey and Massachusetts.”¹³⁹⁷ What happened is that, “following the federal approvals, the medication must be moved through the state and local regulatory processes. In the case of LAAM, however, neither the state nor the local agencies were prepared for the introduction of a new opioid management agent. The extensive and time-consuming approval process that followed the FDA approval clearly reduced the initial momentum and enthusiasm for bringing the new medication into the addiction treatment system.”¹³⁹⁸

Psychedelic psychotherapy would be practiced by individual physicians in private practice. Even when used in the treatment of drug abuse, psychedelic psychotherapy would not need to be adopted by state and local treatment systems, which may have entrenched interests favoring the status quo. Nevertheless, obtaining approval for psychedelic psychotherapy may still face resistance in many state legislatures, suggesting that there will be a substantial time-lag between federal approval and widespread implementation.

¹³⁹²Henry J. Methadone: Where are we now? *Hosp Med* 60 (1999) 3:161-164.

¹³⁹³Sneyd R. House approves methadone treatment plan. Associated Press, May 1, 2000. The bill “requires that methadone clinics can only operate at hospitals. It also includes language requiring that alternatives to methadone, itself an addictive drug, be promoted at the clinics once they're available.

¹³⁹⁴Staff. National Alliance of Methadone Advocates (NAMA) Alert. May 3, 2000. www.methadone.org

¹³⁹⁵Mississippi, Idaho, Montana, North Dakota, South Dakota, West Virginia, and Wyoming.

¹³⁹⁶Rawson R, Hasson A, Huber A, McCann M, Ling W. A 3-Year Progress Report on the implementation of LAAM in the United States. *Addiction* 93 (1999) 4:533-540.

¹³⁹⁷*Ibid.*, 535.

¹³⁹⁸*Ibid.*, 538.

Bifurcated Scheduling

There is one novel regulatory response that avoids the slow state by state process of moving a Schedule I controlled substance that has been approved by FDA for medical purposes from Schedule I to Schedule II. This strategy was first implemented in the recent scheduling by Congress of the “date-rape, club drug” GHB.¹³⁹⁹ Approved as a prescription medicine in some countries in Europe,¹⁴⁰⁰ GHB is also being researched within the United States as a valuable drug in the treatment of narcolepsy, with the filing of a New Drug Application (NDA) expected in the fall of 2000.¹⁴⁰¹ Remarkably, Congress placed GHB in Schedule I and Schedule III simultaneously, with the status of each dose of GHB determined by the purpose to which the drug is put.¹⁴⁰² All GHB that is used for non-medical purposes is regulated under Schedule I.¹⁴⁰³ All GHB that is manufactured or used in FDA-approved research protocols is classified under Schedule 1 but the level of controls that are applied are for drugs in Schedule III.¹⁴⁰⁴ If GHB is approved by FDA for prescription use, medical supplies will be placed in Schedule III.¹⁴⁰⁵ As President Clinton commented upon signing the bill scheduling GHB, “The Act will not impede ongoing research into the potential legitimate use of this drug to treat the special needs of those suffering from narcolepsy. Indeed, this Act creates a special exemption that provides that the manufacture and distribution of this drug for properly approved research purposes will be subject to the physical security requirements of Schedule III rather than Schedule I.”¹⁴⁰⁶

In exchange for having GHB placed in Schedule III for medical purposes, its

¹³⁹⁹Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 1999. 106 P.L.172; 114 Stat. 7. February 18, 2000.

¹⁴⁰⁰Kam P, Yoong F. Gamma-hydroxybutyric acid: an emerging recreational drug. *Anaesthesia* 53 (Dec 1998) 12:1195-8.

¹⁴⁰¹Bullion J. President Clinton Signs H.R. 2130 Protecting the Medical use of GHB; Scheduling of Orphan Medical's Xyrem Defined. Orphan Medical Press Release. (February 21, 2000). http://www.orphan.com/press_releases_detail.dbm?ID=106

¹⁴⁰²The FDA official who helped develop this solution was Mr. Mike Klein, formerly of Pilot Drug, then of DACCADP, and at present with the Controlled Substances Staff.

¹⁴⁰³106 P.L 172. Sec 3 (a) (1) Emergency Scheduling of GHB.

¹⁴⁰⁴Sec 3 (a) (1) (A). “For purposes of any requirements that relate to the physical security of registered manufacturers and registered distributors, the final order shall treat such drug, when the drug is manufactured, distributed, or possessed in accordance with an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (whether the exemption involved is authorized before, on, or after the date of the enactment of this Act), as being in the same schedule as that recommended by the Secretary of Health and Human Services for the drug when the drug is the subject of an authorized investigational new drug application (relating to such section 505(i)).”

¹⁴⁰⁵Sec 3 (a) (1) (B).

¹⁴⁰⁶Bullion J. (February 21, 2000).

sponsor, Orphan Medical, has been required to follow a set of measures to control diversion of GHB intended for medical purposes.¹⁴⁰⁷ According to Mr. Michael Perez, Public Relations, Orphan Medical, “We agreed to provide ARCOS [Automation of Reports and Consolidated Order Systems—a DEA data base for auditing the manufacturing and wholesale distribution of Schedule II drugs] monitoring of manufacture and distribution, create a patient registry and track patient usage to make sure it is used within prescribed amounts without diversion. We kept the regulatory impact on the manufacturer and the distributor but not on patients. These kind of provisions are not usually required for Schedule III drugs.”^{1408 1409}

In addition, data that could be used to create a national patient registry must be gathered. The law states, "(5) That each dispensing practitioner shall maintain for each prescription the name of the prescribing practitioner, the prescribing practitioner's Federal and State registration numbers, with the expiration dates of these registrations, verification that the prescribing practitioner possesses the appropriate registration to prescribe this controlled substance, the patient's name and address, the name of the patient's insurance provider and documentation by a medical practitioner licensed and registered to prescribe the drug of the patient's medical need for the drug. Such information shall be available for inspection and copying by the Attorney General.”¹⁴¹⁰

Ms. Patti Engel, Vice President of Orphan Medical, discussed the individual patient registry and indicated that they are sensitive to the need to maintain confidentiality of the list. In addition to tracking patients and treatment outcomes, the list will track the number of patients, what their current prescriptions are, and how much of the drug has been dispensed. The list will then linked to DEA to help it determine the quotas on manufacturing of GHB for medical purposes.¹⁴¹¹ Dr. Dayton Reardon, Vice-President of Regulatory Affairs for Orphan Medical, explained that due to the concern to protect the privacy of the patients, the patient registry is not actually being kept by the company itself but by a third party, the company that handles the distribution of GHB to the pharmacies.¹⁴¹² Though Orphan Medical cannot obtain the names and records of the physicians and patients, DEA, FDA and State Medical Boards retain the right to obtain access to the registry.

Research into the use of GHB for narcolepsy has been completed and the FDA has

¹⁴⁰⁷106 P.L 172. Sec. 4. Authority for Additional Reporting Requirements for Gamma Hydroxybutyric Products in Schedule III.

¹⁴⁰⁸personal communication, Michael Perez, Supervisor of Professional Information Services, Orphan Medical, March 24, 2000.

¹⁴⁰⁹For a review of how one observer analyzed the impact of diversion control regulations on the medical use of GHB prior to the bifurcated scheduling, see Rohde (2000):138-139.

¹⁴¹⁰106 P.L 172. Sec 4 (h) (5)

¹⁴¹¹personal communication, Ms.Patti Engel, Vice-President for Marketing, March 29, 2000.

¹⁴¹²personal communication, Dr. Dayton Reardon, Vice-President of Regulatory Affairs, June 7, 2000.

promised a six-month priority review.¹⁴¹³ If FDA does approve GHB for prescription use for narcolepsy, Orphan Medical still needs to go to the states to have GHB placed in Schedule III. But it does not have to ask that GHB for non-medical purposes be taken out of Schedule I. Placing GHB for medical purposes in Schedule III doesn't involve asking legislators to remove GHB from Schedule I, a psychological hurdle that could have made some state legislators think that they were somehow being asked to be soft on the non-medical use of GHB. Only Congress can create bifurcated scheduling of this sort. Still, what Congress did with GHB creates a precedent for the regulation of the potential medical uses of other Schedule I drugs. If a convincing case can be made that the medical use of a Schedule I drug can be sufficiently controlled, the drug could conceivably be scheduled lower than Schedule II, simplifying its medical use. Ms. Engel reported that "it was very time consuming to get this exemption in the law, to present the data and to attend Congressional committees. However, the legislators were very willing to listen and to propose amendments."¹⁴¹⁴

State Limitations on Off-Label Prescriptions

States, primarily through their medical licensing boards, do regulate the practice of medicine. At least 19 states have chosen explicitly to recognize in their statutes the legality of off-label prescriptions in some contexts.¹⁴¹⁵ Most state statutes are silent about off-label prescribing, thereby setting no barriers to such uses. Though very powerful, the organized resistance from the medical community and patient advocates to controls over the prescription of drugs for off-label uses has not prevailed in every instance. There is one state, South Carolina, that formally prohibits off-label prescriptions, not just of Schedule II drugs but of all controlled substances in Schedules II-V.^{1416 1417 1418} This provision is so

¹⁴¹³Ibid.

¹⁴¹⁴personal communication, Ms.Patti Engel, Vice-President for Marketing, Orphan Medical, March 29, 2000.

¹⁴¹⁵Beck, Azari (1998): 76.

¹⁴¹⁶Cooper J, Czechowicz D, Molinari S. The Impact of Prescription Drug Control Systems on Medical Practice and Patient Care: A Summary of the NIDA Technical Review. in Cooper J, Czechowicz D, Molinari S. (eds.) *Impact of Prescription Drug Diversion Control Systems on Medical Practice and Patient Care*. NIDA Research Monograph Series #131. Washington, DC, NIH Publication # 93-3507, 1992: 2.

¹⁴¹⁷South Carolina Code §44-53-360 Narcotics and Controlled Substances. Prescriptions. South Carolina's statute reads, "No practitioner shall dispense any controlled substance for any use other than the uses approved by the Federal Food and Drug Administration or unless an investigation of new drug application for the substance has been obtained and approved by the Federal agency and a copy thereof filed with the Department [of Health]. Provided, that the labelling required under federal law to accompany certain drug products (commonly known as the "package insert") shall be prima facie evidence of the approved uses for

broad that the State Board of Medical Examiners has not prioritized the enforcement of this provision and has not prosecuted any physicians solely for prescribing off-label for several decades.¹⁴¹⁹ ¹⁴²⁰ In 1999, a bill to repeal all restrictions on off-label prescriptions was filed in the South Carolina State legislature.¹⁴²¹ Although no action will probably be taken in this legislative session, the bill will be reintroduced in the next session where it will likely pass.¹⁴²² By 2001, off-label prescribing of all controlled substances will probably be legal throughout the United States.

Off-Label Prescriptions: Implications for Medical Use of Psychedelics and Marijuana

Limits on FDA's authority to control off-label prescriptions and DEA's failed efforts to control off-label prescription of Marinol or set arbitrarily low quotas for Ritalin illustrate that neither the FDA nor the DEA has the authority to prohibit prescription for off-label indications, even when a drug is a controlled substance in Schedules II-V. If marijuana or any psychedelic drug is eventually approved by the FDA for use in treatment of a specific indication, no restrictions on off-label uses can be imposed under standard FDA procedures (subject to qualifications discussed below relating to methadone and thalidomide). The DEA's and the FDA's lack of authority to place limitations on off-label uses of prescription drugs will likely reduce their willingness to approve any potential medical uses of marijuana or psychedelics, unless some other form of regulation or agreement would ensure that the prescription use of psychedelic drugs or marijuana would either be limited to the purposes for which they were proven safe and effective, or would be used with substantial care and

such drug, unless other specifically provided by statute or regulation of the Department or State Board of Medical Examiners."

¹⁴¹⁸Even South Carolina has affirmed the appropriateness of off-label prescription of certain drugs which are not controlled substances. South Carolina Code Ann. § 38-71-275 Insurance coverage for certain drugs not to be excluded from policy definitions.(1999) mandates that insurance companies cannot "exclude coverage of any such drug used for the treatment of cancer on the grounds that the drug has not been approved by the Federal Food and Drug Administration for the treatment of the specific type of cancer for which the drug has been prescribed; provided, that such drug is recognized for treatment of that specific type of cancer in one of the standard reference compendia or in the medical literature."

¹⁴¹⁹personal communication, Aaron Kosloski, General Council, South Carolina Medical Association and past Council, State Board of Medical Examiners, May 10, 2000.

¹⁴²⁰personal communication, Mr. Wilbur Harding, Director, Bureau of Drug Control, SC Department of Health and Environmental Quality, May 17, 2000. Mr. Harding indicated that no physician has been prosecuted solely for off-label prescription during the seven years that he has been in his position. He also confirmed that the regulations do indeed apply to all controlled substances in Schedules II-V, not just Schedule II drugs. He was in favor of the bill to eliminate the regulations against off-label prescriptions.

¹⁴²¹S.C. Bill # 959.

¹⁴²²personal communication, Aaron Kosloski. May 10, 2000.

discretion when prescribed off-label.

FDA and DEA cannot prohibit the off-label uses of controlled substances that have been approved for prescription use unless Congress grants those agencies such authority. After FDA approves a Schedule I drug for medical use, each state must also formally approve the rescheduling of that drug from Schedule I to Schedule II to permit its medical use within that state. The bills that will need to be introduced in State legislatures rescheduling a psychedelic drug from Schedule I to Schedule II create a legislative vehicle that could also be used to propose restrictions on off-label use. The fact that only one State has ever limited the off-label use of controlled substances, with that limitation likely to be repealed in the near future, suggests that it is not likely that off-label prescriptions will be prohibited in most or all of those states that follow the lead of the FDA and approve the medical use of a psychedelic drug.

The primary focus of regulations to control misuse, abuse and diversion with respect to psychedelic psychotherapy cannot lie in the control of off-label prescriptions. Control over off-label prescription, even if it could be implemented, would not in any case address the problem of misuse, abuse and diversion from prescriptions written in accordance with the labeled indication.

The most fruitful vehicles for regulatory efforts to minimize misuse, abuse and diversion in psychedelic psychotherapy lies instead in the control of the practitioners themselves, in the establishment of minimum standards for the settings in which these practitioners are permitted to practice, in limitations on the distribution of the drug, and in the creation of a national registry of patients. The question to be addressed next is whether FDA actually has the authority to impose such special restrictions.

Basis of FDA Claims of Authority to Impose Special Restrictions

FDA has asserted the authority to impose special restrictions on the use of drugs that pose special safety risks and also meet the qualifications for designation under the fast track (Subpart E) and accelerated approval programs (Subpart H).¹⁴²³

In 1988, FDA created the fast track Program (Subpart E) to expedite the development of drugs for life-threatening or severely debilitating illnesses for which no adequate medications were available.¹⁴²⁴ The definition of “serious and life-threatening illnesses,” was initially proposed in the “treatment IND” regulations,¹⁴²⁵ which provided access to experimental drugs to patients outside of a controlled trial under certain limited conditions.¹⁴²⁶ In December 1992, FDA created the accelerated approval program (Subpart

¹⁴²³21 CFR 314.520 Approval with restrictions to assure safe use.

¹⁴²⁴Procedures for Drugs Intended to Treat Life-Threatening or Severely Debilitating Illnesses. 1988 Interim Rule. (21 CFR 312.80 through 312.88 (Subpart E). 53 FR 41516 (October 21, 1988).

¹⁴²⁵An important additional element in the treatment IND program was that access to unapproved drugs was permitted only if there were no alternative medicines available. Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Treatment Use and Sale. 52 FR 19466 (May 22, 1987).

H),¹⁴²⁷ which was similar to the fast track program, in order to respond to the dire need for AIDS medications.¹⁴²⁸ To qualify for the accelerated approval program, a drug needed to show potential to treat some aspect of a condition that is serious or life-threatening.¹⁴²⁹ If there were approved treatments for the condition, the drug could still qualify for the accelerated drug approval program if it responded to a medical need that was unmet.¹⁴³⁰ The criteria were the same as for fast track drugs. The innovation in the accelerated approval program was that drugs for serious or life-threatening illnesses for which no adequate medications were available could be approved sooner than was usually the case in the drug review process. Approval could be granted “on the basis of adequate and well-controlled trials establishing that the drug [or biological] product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.”¹⁴³¹ In the case of AIDS drugs, approval could be based on reduced viral loads, as opposed to the more difficult and time-consuming standard endpoint of enhanced survival time.

As part of the accelerated approval program, FDA designed a regulation that gave itself the authority to impose special controls on prescription drugs “whose safe and effective use requires limitations on distribution or use.”¹⁴³² Mechanisms of control would include the option to “(1) restrict distribution to certain facilities or to physicians with special training or experience, or (2) condition distribution on the performance of specified medical procedures.”¹⁴³³ Though the regulations giving FDA authority to impose special controls on

¹⁴²⁶The treatment IND program and the expedited access program were often accompanied by a requirement that the drug sponsor carry out post-approval studies on various aspects of the performance of the drug. These studies were called Phase IV studies. Finkel M. Phase IV Testing: FDA Viewpoint and Expectations. 33 *FDC L* 181 (1978). Mattison N, Richard B. Postapproval Research Requested by the FDA at the time of NCE Approval, 1970-1984. *Drug Info J* 21 (1987): 309.

¹⁴²⁷New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval. 57 Fed Reg 58942 (December 11, 1992).

¹⁴²⁸The accelerated approval program was created in response to pressure from AIDS activists who wanted the FDA to speed up its approval process for medicines to treat AIDS. The activists justified their call for changes in FDA procedure by noting that AIDS was a fatal disease for which there were no effective medications.

¹⁴²⁹Lumpkin M. Accelerating Drug Development: Regulatory Initiatives in the US. DIA EuroMeeting 2000, March 9, 2000. Slide 7. <http://www.fda.gov/cder/present/dia-nice2000/dianice1/sld007.htm>

¹⁴³⁰*Ibid.*, Slide 8. <http://www.fda.gov/cder/present/dia-nice2000/dianice1/sld008.htm>

¹⁴³¹21 CFR 314.510

¹⁴³²57 Fed Reg 58942 (December 11, 1992) Section IV (B- 6).

¹⁴³³21 CFR §314.520 and 601.41.

prescription drugs appear only in the Subpart H section of the regulations, FDA chose not to limit the scope of these regulations only to Subpart H drugs in the accelerated approval program that had been approved on the basis of surrogate endpoints. FDA designed its new powers to apply to all drugs enrolled into the fast track and accelerated approval programs, as well as to all drugs “that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g. ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy),” regardless of whether or not the drugs have been formally entered into either the fast track or accelerated approval program.¹⁴³⁴ ¹⁴³⁵ For example, in September 1997, FDA approved the medical use of thalidomide for the treatment of erythema nodosum leprosum (ENL), a complication of leprosy.¹⁴³⁶ FDA claimed authority under the accelerated approval regulations to regulate thalidomide more extensively than any other drug other than methadone.¹⁴³⁷ According to FDA, “ENL is a serious, severe complication of leprosy for which no good alternative therapies are presently available for many people with this disease.”¹⁴³⁸ FDA announced “Because of thalidomide’s potential for causing birth defects, FDA invoked unprecedented regulatory authority to tightly control the marketing of thalidomide in the United States.”¹⁴³⁹ FDA’s authority to impose special controls over the use of thalidomide were claimed to stem from the Subpart H regulation, even though the approval of thalidomide was not based on surrogate endpoints but on standard outcome measures.¹⁴⁴⁰

¹⁴³⁴21 CFR 314.500 Scope. 57 FR 58942 (December 11, 1992). At 64 FR 402 (January 5, 1999), Sec. 314.500 was amended by removing the phrase “and antibiotic”, effective May 20, 1999.

¹⁴³⁵In addition to the fast track and accelerated approval programs, FDA also has a system of priority review. Drugs can qualify for priority review “if they provide a significant improvement compared to marketed products in the treatment, diagnosis or prevention of a disease, eligibility is not limited to drugs for a serious or life-threatening disease.” (FDA Guidance- Fast Track Drug Development Programs – Designation, Development and Application Review. September 1998. Procedural 9.) The priority review program is not associated with regulations providing FDA the authority to impose special restrictions as a condition of approval.

¹⁴³⁶FDA Talk Paper T97-44 Sept. 22, 1997 FDA Issues Approvable Letter to Celgene for Thalidomide, <http://www.fda.gov/bbs/topics/ANSWERS/ANS00820.html>

¹⁴³⁷21 CFR 314.520.

¹⁴³⁸FDA Talk Paper T97-44 Sept. 22, 1997.

¹⁴³⁹Thalidomide Information Page, FDA/CDER <http://www.fda.gov/cder/news/thalinfo/default.htm>

¹⁴⁴⁰ FDA commented, “At least 70-80 percent of patients with ENL responded to thalidomide therapy with improvements in skin lesions as assessed in double blind, controlled clinical trials, compared to approximately 25 percent of patients given placebo.” FDA Talk Paper T97-44 Sept. 22, 1997 FDA Issues Approvable Letter to Celgene for Thalidomide, <http://www.fda.gov/bbs/topics/ANSWERS/ANS00820.html>

In proposing these additions to its regulatory arsenal, FDA may be looking to Europe as a model. The European Agency for the Evaluation of Medicinal Products, the organization that regulates pharmaceutical drugs for a population of about 360 million Europeans, has the legal authority to restrict the prescription of certain drugs to physicians with special expertise or training and to limit distribution only to hospital pharmacies.¹⁴⁴¹

FDA's assertion that it has the authority to impose additional restrictions on certain drugs is of significance to the regulation of marijuana and the psychedelics. In the context of the accelerated approval program, FDA commented that "drugs for the treatment of depression and psychosis would be examples of those that could be covered by the accelerated approval program," especially if they carried unusual safety risks.¹⁴⁴²

Psychedelics have been proposed for the treatment of depression and psychosis,¹⁴⁴³ though only in closely monitored situations that offer the opportunity for prolonged post-treatment supervision and therapy. This application might be exactly the type of medical treatment that is not safe unless there are additional restrictions on use within certain facilities with specially trained personnel.¹⁴⁴⁴

¹⁴⁴¹Article 3, part 3 of the Council Directive 92/26/EEC of March 31, 1992, Official Journal of the European Communities No L 113/5 states that "the competent authorities may fix sub-categories for medicinal products which are available on medical prescription only. In that case, they shall refer to the following classification: ...(c_ medicinal products on restricted medical prescription, reserved for use in certain specialized areas." Article 3, part 3 expands by noting, "Where members provide for the sub-category of medicinal products subject to restricted prescription, they shall take account of the following factors: —the medicinal product, because of its pharmaceutical characteristics or novelty or in the interests of public health, is reserved for treatments which can only be followed in a hospital environment,—the medicinal product is used in the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow-up may be carried out elsewhere, or—the medicinal product is intended for outpatients but its use may produce very serious side-effects requiring a prescription drawn up by a specialist and special supervision throughout the treatment." Richard Kingman, who kindly drew my attention to this feature of the European drug approval process, reported that this regulation was entirely noncontroversial, and neither the British Medical Association nor the Royal Pharmaceutical Society of Great Britain included a reference to this section in their testimony on medical issues before the Select Committee on the European Communities of the UK House of Lords. Mr. Kingman speculated that that lack of controversy may have been due to the fact that the health systems in Europe are "either administered as a public entity or heavily regulated by public authorities. Thus, if the decision is made that a drug should be restricted to specialist centers, this can [already] be done by administrative action through the health services, rather than the medicines approval process." Letter of January 10, 1997. For more information on the European system of drug approval, see FDA Reform and the European Medicines Evaluation Agency, 108 Harv. L Rev. 2009. June 1995.

¹⁴⁴²57 Fed Reg 58942 (December 11, 1992) Section IV (B- 6).

¹⁴⁴³Grof S. *LSD Psychotherapy*. Pomona, CA: Hunter House, 1980.

¹⁴⁴⁴One example in which a physician requires special training and experience before being licensed to

Marijuana for the treatment of AIDS wasting syndrome would be considered a drug for the treatment of a life-threatening illness, since patients with advanced cases of AIDS were specifically identified as having immediately life-threatening illnesses. The advent of protease inhibitors that prevent AIDS wasting would probably limit the use of marijuana only to patients whose wasting syndrome was not successfully treated with those drugs. Marijuana for the treatment of nausea and vomiting associated with cancer chemotherapy would qualify in the subset of patients for whom existing antiemetic medications do not adequately control the side effects of chemotherapy. Marijuana for the treatment of spasticity might not qualify, because spasticity is not life-threatening and the symptoms do not lead to additional morbidity. Marijuana for the treatment of glaucoma might qualify, since blindness is a serious outcome, though the marijuana would need to be the treatment of last resort, since there are already other medications approved for glaucoma.

Mr. Eric Katz, Senior Policy Analyst for the US Public Health Service, questioned FDA's assertion of its new authority when he wrote in 1993 that, "The FDA can and has imposed such limits [on appropriate uses] on drug labeling but is powerless in this regard once the drug enters commerce."¹⁴⁴⁵ FDA promulgated its regulations for the accelerated approval process despite the fact that a judicial ruling in *American Pharmaceutical Association v. Weinberger* explicitly rejected FDA's argument that it had statutory authority to impose restrictions on the distribution of prescription drugs.

The FDA tried to justify the limits it claimed it could impose on prescription drugs in its accelerated approval program by distinguishing its assertions of statutory authority from those rejected in the decision in *American Pharmaceutical Association v. Weinberger*.¹⁴⁴⁶ In that case, the Court had ruled that the FDA had no right to limit the distribution of a drug that was safe when used as approved, even though there was a risk of misuse. When issuing the accelerated approval regulations, FDA claimed that, "The Court of Appeals determined that the type of misuse associated with methadone, i.e. misuse by persons who have no intent to try to use drugs for medical purposes, differed from safety issues contemplated for control under [the accelerated approval program]... The restrictions under these provisions would be imposed on the sponsor only as necessary for safe use under the

prescribe a drug is with the use of radioactive drugs in nuclear medicine. These special requirements however, are imposed not by the FDA but by the Nuclear Regulatory Commission, which has independent jurisdiction over the use of these medicines. 50 FR 30616 (July 26, 1985), 47 Fed Reg 3228 (January 22, 1982) and 47 Fed Reg 54376 (December 2, 1982).

¹⁴⁴⁵Katz E. Europe's Centralized New Drug Procedures: Is the United States Prepared to Keep Pace? 48 *Food Drug Cosm L J* 577 (1993): 584.

¹⁴⁴⁶37 FR 6940 (April 6, 1972); 37 FR 26790 (December 15, 1972). Both of these regulations attempted to control the distribution of methadone but were later withdrawn as a result of the decision in *American Pharmaceutical Assn. v. Weinberger*, 377 F. Supp. 824 (D.D.C. 1974), *affd. sub. nom.*, *American Pharmaceutical Assn. v. Mathews*, 530 F. 2d 1054 (D.C. Cir. 1976).

extraordinary circumstances of the particular drug and use. Without such restrictions, the drugs would not meet the statutory criteria, could not be approved for distribution and would not be available for prescribing or dispensing.”¹⁴⁴⁷ Though somewhat compelling, this argument sounds similar to the unsuccessful argument made by DEA when it claimed that Marinol was not safe for distribution unless additional restrictions were placed restricting any off-label uses.

According to Mr. Peter Hutt, an attorney with experience litigating the limits of FDA authority, FDA may well be overreaching in its promulgation of these regulations, which might not withstand legal challenge. No test cases challenging FDA’s authority to approve a drug with special restrictions have arisen, in part because thalidomide is the first instance in which requirements for specialized training or experience have been formally imposed in the United States under the accelerated approval program regulations.^{1448 1449} Legal challenge to the thalidomide regulations is unlikely due to a widespread public consensus supporting the fundamental need to prevent fetal exposure to thalidomide. Legal challenge is also unlikely, since the training that is required to prescribe thalidomide is relatively minimal. Any physician who wants to participate in prescribing thalidomide can do so without much time or trouble.¹⁴⁵⁰

Possible Challenges to FDA Authority to Impose Restrictions on Psychedelic Psychotherapy

The training that will be proposed in this Chapter for physicians before they will be permitted to deliver psychedelic psychotherapy will be much more extensive than the minimal training required to prescribe thalidomide. The limitations on the prescription of thalidomide had to do with relatively simple but comprehensive precautions to prevent exposing a fetus to thalidomide. Only physicians who complete this training are permitted to prescribe it. The training that will be required for the prescription of a psychedelic drug as an adjunct to psychotherapy will involve the teaching of a new method of treatment. Furthermore, this Chapter will propose that the prescription of psychedelic psychotherapy be limited only to board-certified psychiatrists, excluding general practitioners, neurologists and all other physicians from prescribing psychedelics.¹⁴⁵¹ The more extensive nature of

¹⁴⁴⁷57 Fed Reg 58942 (December 11, 1992) Sec 3, (E - paragraph 20).

¹⁴⁴⁸personal communication, Peter Hutt, January 16, 1997.

¹⁴⁴⁹Special restrictions have also been placed on the use of the drug Chymopapain, owned by Knoll. Chymopapain is used for the treatment of documented herniated lumbar intervertebral discs. FDA has required that it be used only in a hospital setting by physicians experienced and trained in the diagnosis of lumbar disc disease and all acceptable treatment modalities including surgery and the management of all potential complications. Facts and Comparisons, St. Louis: Steven Hebel Publishing, January 2000.

¹⁴⁵⁰Frequently Asked Questions Concerning Thalidomide. “17. How do physicians/pharmacies enroll in the S.T.E.P.S. program? Physicians and pharmacies will receive a mailing from Celgene, which will include instructions on how to register in the program.” <http://www.fda.gov/cder/news/thalinfo/thalfaq.htm>

these proposed restrictions could increase the incentives for some physicians to file a legal challenge to FDA's authority to insist on special training requirements. Legal challenge to FDA's authority to impose special restrictions might also come from parties that were opposed to the medical use of marijuana or psychedelics and saw such special restrictions as a necessary component of FDA approval of those drugs. Challenge could also come from parties that were opposed on principle to the expansion of FDA's authority.¹⁴⁵² FDA's authority to impose special restrictions could conceivably be subjected to legal challenge even by the sponsor, although the incentives of the sponsor would be to support the restrictions in order to expedite the approval process and to limit misuse, abuse and diversion of its drug.

The authority claimed by FDA to be able to impose special restrictions on the potential prescription use of drugs as a result of provisions in the accelerated approval program remains unchallenged.¹⁴⁵³ As a result, it would be unwise to base any proposed regulatory framework for psychedelic psychotherapy only on the accelerated approval provisions, at least until their legal status is clarified. Therefore, a voluntary system of controls accepted by the sponsor will also be proposed to supplement FDA authority under the accelerated approval provisions.

Voluntary Limits on the Prescription Use of Psychedelics

When FDA initially promulgated its regulations for the accelerated approval program, it made the remarkable statement that "the restrictions on use will be tailored to the specific safety issue raised by the particular drug or biological product and *agreed to by the applicant at the time of approval*(emphasis added)."¹⁴⁵⁴ The inclusion of the statement about obtaining the agreement of the applicant points the way to a little-known aspect of FDA regulation - voluntary agreements signed by the drug sponsor as a condition of getting a drug approved for marketing. Just how voluntary these agreements are is open to question,

¹⁴⁵¹Alternatively, a performance test of sorts could be developed to evaluate any physician interested in prescribing psychedelics. This is not the option recommended for reasons to be discussed later in this chapter.

¹⁴⁵²Whether these parties would have standing to sue is another issue.

¹⁴⁵³FDA's proposed restriction of prescribing authority of RU-486 to doctors who can perform surgical abortions may generate a legal challenge, if negotiations between the sponsor, the Population Council, and FDA do not remove this restriction. According to Dr. Wendy Chavkin, a professor of public health at Columbia University, "To encumber a drug like this is extremely unusual for the FDA... We have Viagra that went out in widespread fashion even though there was some suggestion that it might cause serious cardiovascular events. In contrast, this is a highly studied drug where the safety and efficacy have been demonstrated. That indicates how the political climate is really interfering in the science." Stolberg S. FDA Adds Hurdles in Approval of Abortion Pill. *NY Times* (June 8, 2000):A18.

¹⁴⁵⁴57 Fed Reg 58942 (December 11, 1992), II (D).

given the asymmetries in the balance of power between the FDA and the sponsor at the time of NDA review.¹⁴⁵⁵ Most agreements between sponsors and the FDA are specified in the approval letters, which are made public. How these agreements were reached is much more difficult to determine.

Sponsors of the medical use of marijuana and psychedelics may be willing to accept a wide range of controls in the context of voluntary agreements, making it possible to implement a wide range of policy options. If the regulatory controls that FDA decides to impose are supplemented by voluntary agreements, as solid a legal framework as possible, short of new Congressional action, will be created for the enforcement of the restrictions. Mutual agreements between the FDA and the sponsors of the medical use of marijuana or psychedelics offer the best opportunity to create a system of regulatory controls that will permit the medical benefits of these drugs to be realized, while ensuring the minimization of misuse, abuse and diversion.

Regulatory Authority for Restrictions on Advertising of Approved Medical Uses

Under current FDA regulations, pharmaceutical companies can advertise any of their approved drugs to medical professionals or direct to consumers, regardless of whether the drugs are in Schedule II and considered to have a high potential for abuse or are over-the-counter drugs with a low potential for abuse.^{1456 1457 1458} FDA regulations do govern the type and amount of information that can be communicated, but FDA has no authority to limit advertising as long as it meets four basic criteria: “1) it is not false or misleading in any respect..., 2) presents a fair balance between information about effectiveness and risk, 3) includes a thorough major statement conveying all of the products’ most important risk information in consumer-friendly language, 4) communicates all information relevant to the products’ indication in consumer-friendly language.”¹⁴⁵⁹ If FDA were to approve a form of

¹⁴⁵⁵Discussing FDA’s system of obtaining voluntary agreement from sponsors for Post-Approval Research (PAR, also known as Phase 4 studies), some students of FDA have noted, “the operation of this PAR system depends primarily on the voluntary cooperation of the sponsoring company... However, this may suggest more willing compliance by the industry than in fact is the case. According to representatives of the industry, firms generally agree to PAR as an expediency – failure to do so, they believe, would result in long delays in approving the drug.” Mattison N, Richard B. Postapproval Research Requested by the FDA at the Time of NCE Approval, 1970-1984. *Drug Info J* 21 (1987): 309.

¹⁴⁵⁶21 CFR 202 Prescription Drug Advertising. For FDA’s most recent statement on direct-to-consumer advertising, see FDA Guidance For Industry Consumer-Directed Broadcast Advertisements, August 1999. <http://www.fda.gov/cder/guidance/1804fnl.pdf> and <http://www.fda.gov/cder/guidance/1804q&a.htm>

¹⁴⁵⁷Council on Ethical and Judicial Affairs of the American Medical Association. Direct-to-Consumer Advertisements of Prescription Drugs. *Food Drug Law J* 55 (2000) 1:119-124.

¹⁴⁵⁸Reeves K. Direct-to-Consumer Broadcast Advertising: Empowering the Consumer or Manipulating a Vulnerable Population? *Food Drug Law J* 53 (1998) 4:661-679.

psychedelic psychotherapy, it would have no ability to prohibit the sponsor from advertising its approved use. If FDA wanted to place limits on such advertising, the limits would need to be voluntarily accepted by the sponsor.

Even FDA's authority to limit the information that pharmaceutical companies can present to physicians about off-label indications, granted to FDA by Congress in the Food and Drug Modernization Act of 1997 (FDAMA),^{1460 1461 1462} has been held to be unconstitutional by the Courts.^{1463 1464} The D.C. District Court ruled, "The government, however benign its motivation, simply cannot justify a restriction of truthful nonmisleading speech on the paternalistic assumption that such restriction is necessary to protect the listener from ignorantly or inadvertently misusing the information."¹⁴⁶⁵

The issue of concern in regard to advertisements for the medical use of a psychedelic drug as an adjunct to psychotherapy is whether the public dissemination of that information will stimulate non-medical use of the substance, with the possibility that some amount of harm to the public health will result. Alternatively, the medical use of a psychedelic "might discourage non-medical use by associating the drug with often-painful treatment rather than with pleasure."¹⁴⁶⁶ However, advertisements would not be likely to emphasize any emotionally painful aspects of psychedelic psychotherapy. Any harmful impact on public health caused by advertising would need to be balanced against public health benefits resulting from the advertising. Ads targeted to the specific patient group for which psychedelic psychotherapy has been approved can stimulate patient interest in the newly approved treatment, with successful treatments generating public health benefits. In advertisements to patient groups, the fear of generating non-medical use seems somewhat reduced, since legal opportunities that could be covered by insurance are being offered for the drug treatment.

¹⁴⁵⁹Consumer-Directed Broadcast Advertisements, August 1999: 2.

¹⁴⁶⁰Food and Drug Administration Modernization Act of 1997. 105 PL 115 §401, Dissemination of information on new uses.

¹⁴⁶¹63 Fed Reg 64556-88 (November 20, 1998) Dissemination of information on unapproved/new uses for marketed drugs, biologics, and devices--FDA Final Rule.

¹⁴⁶²Bass I, Kalb P, Berenson B. Off-Label Promotion: Is FDA's Final Guidance on Industry-Supported Scientific and Educational Programs Enforceable? *Food Drug Law J* 53 (1998) 2:193-212.

¹⁴⁶³Washington Legal Foundation v. Friedman, Civ. No. 94-1306. slip op. (D.D.C. July 30, 1998). Washington Legal Foundation v. Henney and Shalala, 56 F. Supp. 2d 81 (D.D.C. 1999)..

¹⁴⁶⁴Gibbs J. First Amendment Limits on Regulating Information: An Initial Reaction to the *Washington Legal Foundation* Case. *Food Drug Law J.* 53 (1998) 4:597-601.

¹⁴⁶⁵Washington Legal Foundation v. Henney and Shalala, 56 F. Supp. 2d 81 (D.D.C. 1999).

¹⁴⁶⁶Kleiman M. Proposed Therapeutic Uses of MDMA: Risks and Benefits in Decisions about Research Approval and Approval as Medicine. Talk at Conference on Clinical Research with MDMA and MDE. Dead Sea, Israel. Sept 1, 1999. <http://www.maps.org/research/mdma/israel/kleimantalk.html>

As discussed in Chapter 4, it is reassuring to see that there has been a slight decline in non-medical use patterns for marijuana since 1996 on both state and national levels even though there has been massive publicity about successful state initiatives legalizing marijuana's medical uses. Of course, it cannot be determined whether these slight declines would have been even larger in the absence of the substantial amounts of information in the media about the medical uses of marijuana.

Regardless of what the actual net public health impact would be of advertisements about the medical use of psychedelic psychotherapy, FDA is powerless to prohibit the ads. Any regulations on advertisements of psychedelic psychotherapy would need to be the subject of a voluntary agreement between FDA and the sponsor. Voluntary agreements can still be enforced, with companies with products in the development pipeline being especially unlikely to try to renege or violate agreements with FDA.

Regulatory Design by Analogy

The next section of this chapter will focus on the regulation of methadone, thalidomide and electroconvulsive therapy (ECT). The regulation of these medical treatments will be analyzed in an effort to derive lessons from those cases that may prove instructive in the design of a regulatory system for psychedelic psychotherapy. These lessons will be used as a basis for the elaboration of a regulatory system for psychedelic psychotherapy that will follow the analysis of these cases.

Restrictions on Medical Practice: The Methadone Exception

The major exception to the limitations in FDA and DEA authority to regulate the practice of medicine is the unusually detailed and intrusive regulation of the medical use of methadone in the treatment of narcotic addiction.¹⁴⁶⁷ Virtually every aspect of the use of methadone in the treatment of narcotic addiction has been regulated, including specific restrictions on dosages, patient selection and retention, time limits for short-term and long-term detoxification, criteria for take-home dosages, facilities for distribution, organizational structure, training of staff, staff/patient ratios, frequency and type of urine or blood testing of subjects, required counseling and health services, recordkeeping, HIV counseling requirements, and so on.

The legal justification for this exceptional set of regulations is that FDA and DEA are acting under special authority granted by Congress to the Secretary of Health and Human Services and the Attorney General, as part of the Controlled Substances Act of 1970.¹⁴⁶⁸ The relevant section of law was very simple, stating that "The Secretary of Health,

¹⁴⁶⁷21 CFR 291 Drugs Used for Treatment of Narcotic Addicts. 291.501 Narcotic drugs in the maintenance treatment of narcotic addicts. 291.505 Conditions for the use of narcotic drugs; appropriate methods of professional practice for medical treatment of the narcotic addiction of various classes of narcotic addicts under section 4 of the Comprehensive Drug Abuse Prevention and Control Act of 1970.

¹⁴⁶⁸Controlled Substances Act of 1970. Title 1, Sec. 4 Medical Treatment of Narcotic Addiction.

Education and Welfare, 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 classes of narcotic addicts, and shall report thereon from time to time to Congress.”¹⁴⁶⁹ These methods of professional practice have been elaborated in a series of federal regulations over the years.¹⁴⁷⁰

The 1970 statute applies only to the treatment of narcotic addiction. In the context of the Act, a narcotic drug was defined primarily as a derivative of opium or cocaine.¹⁴⁷¹ As a result, the statute contains no legal authority for regulations governing any other prescription use of methadone, such as in the treatment of pain, for which physicians can and do prescribe as they deem necessary. Importantly, the statute does not specifically mention methadone as the only treatment of narcotic addiction. It refers only to “the medical treatment of the narcotic addiction of various classes of narcotic addicts.” Nor does the statute define “medical treatment” in any way.

This statute has important implications for the use of psychedelics to treat heroin or cocaine addiction, a use that has been proposed for ibogaine,¹⁴⁷² LSD,¹⁴⁷³ ketamine,¹⁴⁷⁴ and

¹⁴⁶⁹Ibid.

¹⁴⁷⁰37 FR 6940 (April 6, 1972); 37 FR 26790 (December 15, 1972); 41 FR 28261 (July 9, 1976); 41 FR 17962 (April 29, 1976) ; 42 FR 46698 (September 16, 1977); 42 FR 56897 (October 28, 1977); 45 FR 62694 (September 19, 1980); 48 FR 41049 (September 13, 1983); 52 FR 37046 (October 2, 1987); 54 FR 8954 (March 2, 1989); 54 FR 8973 (March 2, 1989); 54 FR 50226 (December 4, 1989). 58 FR 495 (January 6, 1993); 58 FR 38704 (July 20, 1993—this concerned the addition of LAAM as a drug to be used in the treatment of narcotic addiction). A recent development is described in 64 FR 39810 (July 22, 1999), “The Secretary of the Department of Health and Human Services (the Secretary) (DHHS) is proposing to revise the conditions for the use of narcotic drugs in maintenance and detoxification treatment of opioid addiction. The proposal includes the repeal of the existing narcotic treatment regulations enforced by the Food and Drug Administration (FDA), the creation of a new regulatory system based on an accreditation model under new 42 CFR part 8, and a shift in administrative responsibility and oversight from FDA to the Substance Abuse and Mental Health Services Administration (SAMHSA). This proposal follows a study by the Institute of Medicine (IOM) and reflects recommendations by the IOM and several other entities to improve narcotic addict treatment by allowing for increased clinical judgment in treatment. The proposal is also part of DHHS's Reinvention of Government review.” The most recent proposal for new regulations is 65 FR 125895 (May 4, 2000), Opioid Drugs in Maintenance and Detoxification Treatment of Opiate Addiction; Conditions for the Use of Partial Agonists Treatment Medications in the Office-Based Treatment of Opiate Addiction.

¹⁴⁷¹Controlled Substances Act of 1970. Sec 102 (16).

¹⁴⁷²Mash D, Kovera C, Buck B, Norenberg M, Shapshak P, Hearn L and Sanchez-Ramos J. Medication Development of Ibogaine as a Pharmacotherapy for the Treatment of Drug Dependence. Ali S. (ed.) Neurochemistry of Drugs of Abuse- Cocaine, Ibogaine and Substituted Amphetamine. *Ann N Y Acad Scien* 844 (1998): 274-292.

MDMA.¹⁴⁷⁵ As a result of these statutes, FDA already has sufficient regulatory authority to control virtually every aspect of the use of any psychedelic when used in the treatment of narcotic addiction. FDA can even impose special restrictions on the use in the treatment of narcotic addiction of ketamine, which is already an FDA-approved prescription drug used as an anesthetic. FDA authority would not extend to the use of psychedelics in the treatment of addiction to marijuana, stimulants or depressants, all of which are mentioned in the Act but are explicitly defined in non-narcotic categories, or for the use of psychedelics in the treatment of alcoholism or tobacco addiction, since neither alcohol nor tobacco is covered by the Controlled Substances Act of 1970.

One additional law, the Narcotic Addict Treatment Act of 1974,¹⁴⁷⁶ grants authority to the Attorney General and the Secretary of Health and Human Services to regulate the treatment of narcotic addiction. This law defines detoxification treatment to be the use of a narcotic drug for a period of 21 days or less, and maintenance treatment to be the use of a narcotic drug for a period in excess of 21 days. While the Controlled Substances Act only permitted the regulation of the medical treatment of narcotic addicts, the Narcotic Addict Treatment Act of 1974 extended controls to the registration of the treatment providers.¹⁴⁷⁷ The language of the Narcotic Addict Treatment Act of 1974 is more specific than that of the Controlled Substances Act and clearly applies only to the use of narcotic drugs in the treatment of narcotic addiction. There is no statutory authority to require special registration of practitioners approved to use non-narcotic drugs (e.g. psychedelic drugs) in the treatment of narcotic addiction, nor is there any authority to require that practitioners of psychedelic psychotherapy in the treatment of narcotic addiction be “determined by the Secretary to be qualified (under standards established by the Secretary)” to engage in such treatment.

¹⁴⁷³Savage C, McCabe O. Residential psychedelic (LSD) therapy for the narcotic addict. A controlled study. *Arch Gen Psychiat* 28 (Jun 1973) 6:808-14.

¹⁴⁷⁴Dr. Krupitsky’s current research into the use of ketamine in the treatment of heroin addicts is described in Chapters 4-5. see also Krupitsky (1999).

¹⁴⁷⁵No clinical trials into the use of MDMA in the treatment of heroin or cocaine addiction have been submitted to regulatory authorities. However, there are numerous anecdotal reports of the effectiveness of MDMA in helping to treat cocaine and heroin addiction.

¹⁴⁷⁶Narcotic Addict Treatment Act of 1974. 93 P.L. 281; 88 Stat. 124. May 14, 1974.

¹⁴⁷⁷*Ibid.* Sec 303. 21 USC §823 (g) The Secretary is required to determine whether the practitioner is “qualified (under standards established by the Secretary) to engage in the treatment with respect to which registration is sought” and whether the practitioner will “comply with standards established by the Secretary (after consultation with the Attorney General) respecting the quantities of narcotic drugs which may be provided for unsupervised use by individuals in such treatment.” The Attorney General is required to determine if the practitioner will comply with “standards established by the Attorney General respecting (A) security of stocks of narcotic drugs for such treatment, and (B) the maintenance of records (in accordance with section 307) on such drugs.

IOM and NIH Review of Methadone Regulations

A systematic review of the regulations governing the medical use of methadone was requested of the Institute of Medicine (IOM) in 1992 by the U.S. Public Health Service.¹⁴⁷⁸ The IOM report, published in 1995, noted that no evaluation of the “underlying assumptions or long-term consequences of the regulations” had been conducted in over twenty years and concluded that the regulations “put too much emphasis on protecting society from methadone, and not enough on protecting society from the epidemics of addiction, violence and infectious diseases that methadone can help reduce.”¹⁴⁷⁹

The IOM report also noted that “there is no compelling *medical* reason, in the committee’s view, for regulating methadone differently from all other medications approved by FDA, including Schedule II controlled substances.”¹⁴⁸⁰ Nevertheless, the IOM report concluded that there were other benefits of the increased regulation of methadone such as helping to “maintain community support for methadone treatment programs... encourage comprehensive care and provide guidance to state authorities, hospitals, and medical practitioners.”¹⁴⁸¹

The IOM report noted that regulations were the principal mechanism by which the FDA, NIDA and DEA controlled the medical use of methadone in the treatment of addiction, even though the legislation left to the discretion of the agencies all decisions about the appropriate mechanisms of control. The IOM report found that the regulations were frequently too rigid and recommended the consideration of alternative mechanisms such as clinical practice guidelines and quality assurance systems.¹⁴⁸² The Committee felt that these alternative mechanisms were not sufficiently developed to justify immediate implementation, but urged that they be considered for possible future use.

The statement that emerged from the 1997 NIH Consensus Conference on methadone also noted the excessive nature of the regulation of methadone and proposed educational approaches for the improvement of treatment practices.^{1483 1484} The NIH Consensus statement concluded,

¹⁴⁷⁸Rettig R, Yarmolinski A, eds. *Federal Regulation of Methadone Treatment*. Washington, DC: Institute of Medicine, National Academy Press, 1995.

¹⁴⁷⁹*Ibid.*,3.

¹⁴⁸⁰*Ibid.*,4.

¹⁴⁸¹*Ibid.*,5.

¹⁴⁸²*Ibid.*, 222-226.

¹⁴⁸³Morey S. NIH Consensus Panel Advocates Increased Access to Treatment for Opiate Addiction. *Am Fam Phys* 58 (September 1, 1998) 3:786-787.

¹⁴⁸⁴The Consensus statement was widely publicized. It was reprinted in *JAMA* 280 (December 8, 1998) 22:1936-1943.

Of critical importance in improving methadone maintenance therapy (MMT) of opiate dependence is the recognition that, as in every other area of medicine, treatment must be tailored to the needs of the individual patient. Current federal regulations make this difficult if not impossible. By prescribing MMT procedures in minute detail, FDA regulations limit the flexibility and responsiveness of the programs, require unproductive paperwork, and impose administrative and oversight costs greater than necessary for many patients. Yet these regulations seem to have little if any effect on quality of MMT care. We know of no other area where the Federal government intrudes so deeply and coercively into the practice of medicine. For example, although providing a therapeutic dose is central to effective treatment and the therapeutic dose is now known to be higher than had been previously understood, FDA's regulations discourage such higher doses. However well intentioned the FDA's treatment regulations were when written in 1972, they are no longer helpful. We recommend that these regulations be eliminated. Alternative means, such as accreditation, for improving quality of MMT programs should be instituted. The U.S. Department of Health and Human Services can more effectively, less coercively, and much less expensively discharge its statutory obligation to provide treatment guidance to MMT programs, physicians and staff by means of publications, seminars, Web sites, continuing medical education and the like.

We also believe that current laws and regulations should be revised to eliminate the extra level of regulation on methadone compared with other Schedule II narcotics. Currently, methadone can be dispensed only from facilities that obtain an extra license and comply with extensive extra regulatory requirements. These extra requirements are unnecessary for a medication that is not often diverted to individuals for recreational or casual use but rather to individuals with opiate dependence who lack access to MMT programs.¹⁴⁸⁵

Methadone Program Variables and Patient Outcomes

Research has been conducted into which attributes of methadone treatment programs are related to treatment outcome.^{1486 1487} One study evaluated 17 clinics in the New York

¹⁴⁸⁵Effective Medical Treatment of Opiate Addiction. *NIH Consensus Statement* 15 (November 17-19, 1998) 6:19-20. <http://odp.od.nih.gov/consensus/cons/mental.htm>

¹⁴⁸⁶Ball J, Ross A. *The Effectiveness of Methadone Maintenance Treatment: Patients, Programs, Services, and Outcomes*. New York: Springer-Verlag, 1991.

¹⁴⁸⁷Langendam M, Van Brussel G, Coutinho R, Can Ameijden E. Methadone Maintenance and Cessation of Injecting Drug Use: Results from the Amsterdam Cohort Study. *Addiction*95 (2000) 4:591-600.

City area with a sample of 1,179 patients treated over a two-year period from January 1, 1989 to December 31, 1990.¹⁴⁸⁸ Controlling for patient variables, reduced heroin use during the first year of treatment was associated with “greater director involvement in patient care and more experience [of the director].” Reduced cocaine use during all years was associated with greater counselor availability and overall assessment of counseling.¹⁴⁸⁹

In addition to specific findings, the study concluded with the general observation that, “programs should have means for measuring key indicators of program quality on a regular basis and for relating those indicators to patient progress in treatment and outcomes. Because all programs within a given treatment modality need similar measures, the federal and state/provincial certifications agencies should take the lead in developing, in cooperation with the programs, practical self-evaluation protocols that would allow programs to monitor their internal quality indicators and make adjustments as required to maintain chosen quality standards.”¹⁴⁹⁰

Regulating Methadone: Lessons for Psychedelic Psychotherapy

The regulation of methadone suggests that careful thought should be given to the advantages and disadvantages of restricting psychedelic psychotherapy to specialized treatment facilities. As both the IOM and NIH reports indicate, overregulation can have a negative impact on overall public health. The primary regulatory reform that is being proposed for the use of methadone in the treatment of narcotic addiction is the shift from clinic-based administration to office-based treatment. Advantages of permitting methadone patients to be treated in physician offices include, “(1) distributed geographic access, (2) avoidance of the stigma associated with attending methadone clinics, and (3) an increased ability to treat comorbidity in this high-risk population.”¹⁴⁹¹ According to one estimate, “methadone maintenance is restricted by federal and state regulations to large specialized clinics that serve fewer than 20% of the heroin-dependent population.”¹⁴⁹²

If psychedelic psychotherapy is required to be practiced only in facilities that meet certain minimum standards, this may indeed reduce access and increase the costs of the treatment, further reducing access. On the other side of the ledger, restricting psychedelic psychotherapy to facilities that meet minimum standards would probably result in increased patient safety, enhanced treatment outcomes and increased public acceptability for legal

¹⁴⁸⁸Magura S, Nwakeze P, Kang S-Y, Demsky S. Program Quality Effects on Patient Outcome during Methadone Maintenance: A Study of 17 Clinics. *Subst Use Misuse* 34 (1999) 9:1299-1324.

¹⁴⁸⁹*Ibid.*, 1314.

¹⁴⁹⁰*Ibid.*, 1317.

¹⁴⁹¹Weinrich M. Provision of Methadone Treatment in Primary Care Medical Practices- Review of the Scottish Experience and Implications for US Policy. *JAMA* 283 (March 8, 2000) 10:1346.

¹⁴⁹²McNeely J, Drucker E, Hartel C, Tuchman E. Office-based methadone prescribing: acceptance by Inner-City Practitioners in New York City. *J Urban Health* 77 (March 2000) 1:96.

access to such treatments.

There are several essential differences between psychedelic psychotherapy and methadone maintenance programs that reduce the costs to patients from restricting treatments to facilities that meet certain minimum standards. The main distinction between the treatments is that patients receiving methadone maintenance do so on a daily basis for extended periods of time. In contrast, psychedelic psychotherapy will likely be administered one to several times, with several weeks or longer between treatment sessions. Psychedelic psychotherapy patients suffer less hardship if they need to travel even long distances to the nearest treatment facility, while travel time is a very important factor to methadone patients. The relatively few treatment sessions with psychedelic psychotherapy as compared to daily methadone maintenance further reduce the overall impact of increased costs associated with treatment in a facility that meets certain minimum standards for facilities and staff.

Careful weighing of the costs and benefits of imposing regulations that govern the details of the practice of psychedelic psychotherapy must also be a consideration. The finding in methadone patients of a positive association between treatment outcome and greater counselor availability raises the question of whether there would be any benefit in mandating a certain minimum number of hours of patient interaction with psychedelic psychotherapy treatment staff. The temptation to micromanage the delivery of psychedelic psychotherapy should be tempered by the realization that both the IOM and NIH reports pointed to excessive regulations on the use of methadone as hindering actual patient care. Detailed regulations specifying exactly how the psychedelic psychotherapeutic treatment should be delivered should be used only after there is a demonstrated need for these regulations.

The suggestion that self-evaluation protocols be developed for methadone providers is worth implementing in the regulation of psychedelic psychotherapy. The task of creating these protocols would ideally become a responsibility shared by FDA and the sponsor/pharmaceutical company seeking to develop the practice of psychedelic psychotherapy.

Restrictions on Medical Practice: The Thalidomide Example

FDA explained its placement of special restrictions on thalidomide by noting, “Because of thalidomide’s potential for causing birth defects, FDA invoked unprecedented regulatory authority to tightly control the marketing of thalidomide in the United States. A System for Thalidomide Education and Prescribing Safety (STEPS) oversight program has been initiated that includes limiting authorized prescribers and pharmacies, extensive patient education about the risks associated with thalidomide and a 100% patient registry. This oversight program is designed to help insure a zero tolerance policy for thalidomide exposure during pregnancy.”¹⁴⁹³

In order to prescribe thalidomide, physicians must participate in the educational

¹⁴⁹³CDER Thalidomide Information Page, <http://www.fda.gov/cder/news/thalinfo/default.htm>

component of the STEPS program and register with that program. The educational and registration programs are administered by Celgene Corporation, the pharmaceutical company marketing thalidomide.¹⁴⁹⁴ All patients, male and female, must comply with rigorous contraceptive procedures, even though it is not known if thalidomide can be found in sperm and, if so, whether it would cause birth defects. Male patients must wear condoms during intercourse, and will be given written and oral warnings. Female patients must use two forms of contraceptive simultaneously.¹⁴⁹⁵ Female patients need to obtain a written report from a physician stating that a negative pregnancy test was conducted within 24 hours of starting the medication. Pregnancy testing for female patients will continue weekly for the first month, then biweekly or monthly thereafter depending on the regularity of their cycles. All patients must register with the pharmaceutical company and participate in patient surveys.

Bruce Williams, Vice President, Celgene Corporation, explained the Thalidomide Fetal Exposure Prevention Program. He reported that, “Key elements of the program are as follows: patient and physician education, pharmacy registration, counseling on effective contraception, regular pregnancy testing protocols, informed consent, prescribing guidelines, and a controlled distribution system. In addition, all patients will be listed in a registry and followed up with a confidential survey to track compliance and fetal exposures.”^{1496 1497}

Of special note is the fact that FDA’s thalidomide regulations contain no prohibition or statement against off-label prescription, due in part to the wide range of conditions it may treat.¹⁴⁹⁸ Pressure on FDA to restrict off-label use came from an organization of victims of thalidomide. Randolph Warren, Chief Executive Officer, Thalidomide Victims' Association of Canada, expressed the view that the “association's position is that thalidomide should only be licensed for the medical condition for which it is approved; for each new intended

¹⁴⁹⁴Celgene has prepared a booklet about thalidomide called Thalomid- Balancing the Benefits and the Risks. [http://www.celgene.com/CelgeneN2.nsf/Media/pdf/\\$FILE/Balancing.pdf](http://www.celgene.com/CelgeneN2.nsf/Media/pdf/$FILE/Balancing.pdf)

¹⁴⁹⁵The regulations that concern the patient’s private sexual behavior cannot actually be monitored. They serve instead to provide a set of clear guidelines for safe behavior.

¹⁴⁹⁶Thalidomide- Potential Benefits and Risks. An Open Public Scientific Workshop Sept 9-10, 1997. Executive Summary. <http://www.fda.gov/oashi/aids/thalexe.html>

¹⁴⁹⁷Celgene has actually obtained a patent of some sort for its monitoring system. personal communication, Mr. Ken Restack, Director of Medical Services, Celgene, June 8, 2000.

¹⁴⁹⁸Ibid. Executive Summary. Dr. Woodcock explained that “a rapid resolution of symptoms of erythema nodosum leprosum (ENL) has been reported in patients administered thalidomide, and it is being evaluated for treating life-threatening diseases such as graft vs. host disease, AIDS wasting, and malignancies. Thalidomide also may be useful in treating immunologic disorders such as systemic and discoid lupus, Behcet's disease, Sjogren's syndrome, Crohn's disease, and rheumatoid arthritis. Additional conditions for which thalidomide is being considered for study include a range of dermatological conditions, macular degeneration, tuberculosis, and aphthous ulcers.”

use, the drug should be required to undergo a new application.”¹⁴⁹⁹ FDA, though sympathetic with the concerns of the Thalidomide Victims' Association of Canada, had no authority to restrict off-label uses and did not make any effort to limit such uses.

Dr. James Allen, Vice President for Science and Technology, American Medical Association, also opposed restrictions on off-label uses. A summary of Dr. Allen's comments prepared by FDA indicated that, in his opinion, “physicians will be concerned about a system that is too restrictive or onerous in terms of paperwork and time required. Dr. Allen feared that such a system would likely be circumvented instead of used. In addition, most physicians feel strongly about having the flexibility to prescribe a drug "off-label" if they believe it to be the treatment of choice for their patient. Another potential problem lies in developing a system for selecting and accrediting physicians to prescribe thalidomide. Dr. Allen believed that the issue of accreditation needs careful discussion. Also problematic for physicians would be a requirement to write a specific diagnosis on a prescription, which physicians would likely view as a breach of doctor/patient confidentiality.”¹⁵⁰⁰

In order to ensure that all possible precautions are taken to prevent thalidomide from causing any additional birth defects, FDA has taken legal action “against distribution of thalidomide through buyers' clubs and other illegal venues.”¹⁵⁰¹ Dr. Guillermo Bierzwinsky, Director, Drug Control Directorate of Mexico, reported that in Mexico, where thalidomide has been licensed since 1988 for ENL, “The drug is manufactured at a single plant and directly distributed to infectious disease physicians and dermatologists. Thalidomide is not sold in drugstores.”¹⁵⁰² Dr. Leo Yoder, American Leprosy Mission, has prescribed thalidomide for more than 20 years. He stated that “there have been no known cases of birth defects in the United States from the use of thalidomide for ENL, although some have occurred in other countries where controls and monitoring plans have been less stringent.” William Zellmer, M.P.H., Vice President, American Society of Health-System Pharmacists, expressed the opinion that “pharmacists should be reimbursed for this additional patient counseling function by the drug manufacturer, and that the compensation should be "built in" to the cost of the drug.”¹⁵⁰³

Ken Restack, Director of Medical Services for Celgene, explained that the patient registry is being operated by a third party, not by the company itself.¹⁵⁰⁴ Celgene pays for the recordkeeping project through a contract with the Sloan epidemiological research

¹⁴⁹⁹Ibid.

¹⁵⁰⁰Ibid.

¹⁵⁰¹Ibid.

¹⁵⁰²Ibid.

¹⁵⁰³Ibid.

¹⁵⁰⁴personal communication, Ken Restack, June 8, 2000.

organization, which is affiliated with a major university, The Sloan researchers maintain the registry and also can intervene directly with patients and physicians if the safety protocols are being violated. The registry is considered a research project and has had to be reviewed and approved by an Institutional Review Board. Mr. Restack noted that to protect the privacy of the patients, the company receives reports only with coded identification numbers instead of names. FDA retains the right to review the patient registry if it chooses to do so.

Thalidomide has been on the market for a year and a half, has been prescribed to about 4-5,000 patients, with no reported cases of birth defects. However, some physicians and patients have complained that they find the program too onerous and time-consuming. As a result, the registration system is in the process of being simplified to reduce the paperwork burden on physicians and to limit the extent of the information on pregnancy-related side effects given to women who are not fertile. Roughly 80% of the patients use thalidomide for cancer treatment, and these patients tend to be past the childbearing stage.¹⁵⁰⁵

Regulating Thalidomide: Lessons for Psychedelic Psychotherapy

Several features of the regulation of thalidomide are worth considering in a regulatory system for psychedelic psychotherapy. The features of most relevance are the requirement of special education for the prescribers, distribution of the drug only to approved prescribers and only by mail direct from the manufacturer, and the registry of all patients treated, with long-term follow-up data gathered on all patients.

Of special note is that the regulatory system for thalidomide is being revised to reduce excessive precautionary practices. The willingness of FDA to reconsider its regulations after they have been tested in practice reduces the long-term costs of erring on the side of caution in the design of the initial restrictions on the prescription use of controversial drugs with special risks.

Restrictions on Medical Practice: The Electroconvulsive Therapy Example

Of all the psychiatric treatments that have been developed over the last 50 years, electroconvulsive therapy (ECT) might be the only one that is more controversial than psychedelic psychotherapy. ECT is a treatment used primarily for patients suffering from “delusional and severe endogenous depressions, acute mania, and certain schizophrenic syndromes.”¹⁵⁰⁶ The ECT treatment as practiced today involves the passing of a brief electric current through the non-dominant side of an anesthetized patient’s brain, generating a seizure without causing physical harm to the patient.¹⁵⁰⁷ The treatment is generally repeated six to twelve times, with two to three treatments per week.¹⁵⁰⁸ When first introduced in

¹⁵⁰⁵personal communication, Ken Restack, June 8, 2000.

¹⁵⁰⁶Electroconvulsive Therapy. *NIH Consensus Statement Online* 1985 Jun 10-12 [cited 2000, May 1]; 5(11): 4. http://odp.od.nih.gov/consensus/cons/051/051_intro.htm

¹⁵⁰⁷Fink M. Meduna and the Origins of Convulsive Therapy. *Am J Psychiat* 141 (1984) 9:1034-1041.

¹⁵⁰⁸Electroconvulsive Therapy. *NIH Consensus Statement Online*.

1938 in Italy by Drs. Cerletti and Bini, “ECT was given without the benefit of anesthesia or muscle relaxants...[it] was frightening to behold and a severe ordeal for both patients and staff.”¹⁵⁰⁹ Dr. Max Fink, ECT’s foremost proponent and scholar, has remarked, “Belief that ECT affects the brain arouses primitive fears that the soul of the individual, one’s inherent individuality and uniqueness, is affected. And the treatment is portrayed by the media as it was first perceived—patients being forced to receive treatment against their will, suffering massive bodily convulsions with consequent fractures and severe confusion, and used by Svengali-psychiatrists to control the excited and aggressive behavior of “maniacs.””¹⁵¹⁰

The public controversy over ECT and the strong reactions to its medical use have resulted in a situation in which ECT has been subjected to a wide variety of regulations. Federally, the machines used to induce the seizures have been regulated by FDA as medical devices.¹⁵¹¹ On the state and local level, ECT has been regulated by at least 43 jurisdictions, with most regulations focusing on requiring written informed consent prior to treatment.¹⁵¹² ¹⁵¹³ ¹⁵¹⁴ In California and Texas, the legislatures went so far as to specify a detailed list of exactly what needed to be included in the informed consent form.¹⁵¹⁵ ¹⁵¹⁶ Other regulations primarily concern “procedures to determine the competency of a patient to consent, limitations on the use of ECT in minors, the competent patient’s right to refuse treatment, and the need for concurrence on the appropriateness of ECT by a second psychiatrist.”¹⁵¹⁷

ECT was prohibited entirely within Berkeley, California.¹⁵¹⁸ The ordinance was

¹⁵⁰⁹Lebensohn Z. The History of Electroconvulsive Therapy in the United States and Its Place in American Psychiatry: A Personal Memoir. *Comp Psychiat* 40 (May/June 1999) 3:176-177.

¹⁵¹⁰Fink M. Impact of the Antipsychiatry Movement on the Revival of Electroconvulsive Therapy in the United States. *Electroconvulsive Therapy. Psychiat Clinics Nor Am* 14 (1991) 4:793.

¹⁵¹¹*Ibid.*, 796.

¹⁵¹²Leong G, Eth S. Legal and Ethical Issues in Electroconvulsive Therapy. *Psychiat Clinics Nor Am* 14 (1991) 4:1007-1020.

¹⁵¹³Taub S. Electroconvulsive therapy, malpractice, and informed consent. *J Psychiat Law*(Spring 1987): 7-54.

¹⁵¹⁴Slovenko R. The right of the mentally ill to refuse treatment revisited. *J Psychiat Law* (Fall 1992) 407-434.

¹⁵¹⁵Cal. Welf.& Inst. Code §5326.2 and Tex. Health § Safety Code §578.003 Consent to Therapy.

¹⁵¹⁶If psychedelic psychotherapy becomes approved by FDA, the use of informed consent forms would not be necessary since the treatment would no longer be considered experimental. In practice, an informal consent process is a key component of the preparation each patient receives for the treatment sessions. The therapist works to help each patient develop a voluntary intention to experience whatever emotions may arise during the session. The patient’s ability to accept the psychological processes that are catalyzed is an important contributing factor in treatment outcome.

¹⁵¹⁷Leong, Eth (1991).

subsequently overturned by the Court of Appeals which ruled it unconstitutional, stating, “by enacting an outright, unconditional ban on the administration of ECT within its own borders, Berkeley has created an apparent conflict with the state legislative statutory scheme and its guarantee to all mentally ill persons of a “right to treatment services which promote the potential of the person to function independently.”¹⁵¹⁹

Reporting of Each ECT Treatment Session

In Texas,¹⁵²⁰ California,¹⁵²¹ and Massachusetts,¹⁵²² regulations were issued requiring reports on all ECT treatments to be submitted for review to state authorities. The legal issue of whether the California statute unconstitutionally infringed on the privacy of the patients receiving ECT was evaluated and rejected by one author, who concluded, “to invalidate ECT laws on nebulous privacy or liberty grounds and pave the way for an untoward increase of this potentially devastating treatment would not only deprive the mentally ill of a fairly won political victory, but would exalt the form of individual rights over its substance.”¹⁵²³ No statutes requiring the reporting of information about ECT treatment sessions have been overturned on privacy grounds.

In California, a review of the records of 18,627 patients who received a total of 99,425 treatments between 1977 and 1983 indicated that ECT was administered in a safe manner, but at a per capita rate that was roughly half of that in Massachusetts.¹⁵²⁴ The author

¹⁵¹⁸Berkeley City Ordinance 5504, adopted November 2, 1982. The ordinance prohibited the “administration of electric shock treatment to any person within the City of Berkeley.”

¹⁵¹⁹Northern California Psychiatric Society et al. v. Berkeley, 178 Cal. App. 3d 90, 223 Cal. Rptr. 609 (1986).

¹⁵²⁰Tex. Health & Safety Code 578.007 Reports. (b) A report must state for each quarter: (1) the number of patients who received the therapy, including: (A) the number of persons voluntarily receiving mental health services who consented to the therapy; (B) the number of involuntary patients who consented to the therapy; and (C) the number of involuntary patients for whom a guardian of the person consented to the therapy; (2) the age, sex, and race of the persons receiving the therapy; (3) the source of the treatment payment; (4) the average number of nonelectroconvulsive treatments; (5) the average number of electroconvulsive treatments administered for each complete series of treatments, but not including maintenance treatments; (6) the average number of maintenance electroconvulsive treatments administered per month; (7) the number of fractures, reported memory losses, incidents of apnea, and cardiac arrests without death; (8) autopsy findings if death followed within 14 days after the date of the administration of the therapy; and (9) any other information required by the department.

¹⁵²¹Cal. Welf. & Inst. Code §5326.15 Reports are to be submitted quarterly to the local mental health director, who is to forward a copy to the State Director of Mental Health.

¹⁵²²Massachusetts Mental Health Regulation 181 (effective May 1, 1973). Repealed, no reporting requirement at present.

¹⁵²³Whitcomb D. The Regulation of Electroconvulsive Therapy in California: The Impact of Recent Constitutional Interpretations. *Golden Gate L Rev* 18 (Summer 1988) 2: 494.

speculated that “the laws in California governing ECT administration are so complex and cumbersome that it is likely that many physicians truly do not know what to do to avoid running afoul of the law.”¹⁵²⁵ ¹⁵²⁶

In Texas, 2583 reports about 15,240 treatment sessions that were administered between September 1993 and April 1995 were reviewed.¹⁵²⁷ The report concluded that ECT was generally safe and effective but that “ECT in Texas is performed by a small minority of psychiatrists and is unavailable to many patients who need it.”¹⁵²⁸ The report noted that patients in state hospitals were underrepresented in the sample and that, “reasons may be found in Texas’s complex consent process, which makes it extremely difficult for a psychotic or incompetent patient to qualify for the treatment without extensive guardianship procedures. This problem is not new; incompetent patients have often been denied ECT, even as a treatment of last resort.”¹⁵²⁹ ¹⁵³⁰

The regulation of ECT in Massachusetts required that detailed reports be submitted to the Massachusetts Department of Mental Health (DMH) about each treatment that took place in DMH-licensed facilities.¹⁵³¹ In a study comparing standards of practice for ECT as

¹⁵²⁴Kramer B. Use of ECT in California, 1977-1983. *Am J Psychiat* 142 (October 1985) 10:1190-1192.

¹⁵²⁵*Ibid.*, 1192.

¹⁵²⁶The current regulations (Cal. Welf § Inst. Code §5326.15) have been simplified and only require the reporting of the numbers of patients treated, in four categories, 1) involuntary patients who gave informed consent, 2) involuntary patients deemed incapable of giving informed consent who received treatment against their will, 3) voluntary patients who gave informed consent, and 4) voluntary patients deemed incapable of giving informed consent. The requirement to report patient demographic data, side effects, and funding source have been eliminated. The detailed description of what the informed consent form needs to include has not been changed. §5326.2 Information for Informed Consent.

¹⁵²⁷Reid W, Keller S, Leatherman M, Mason M. ECT in Texas: 19 Months of Mandatory Reporting. *J Clin Psychiat* 59 (January 1998) 1:8-13.

¹⁵²⁸*Ibid.*, 8.

¹⁵²⁹*Ibid.*, 11.

¹⁵³⁰Fortunately, the issue of obtaining consent from incompetent patients for psychedelic psychotherapy is simple to resolve. For all foreseeable treatments, voluntary consent to participate from a patient competent to give that consent would be a required prerequisite for treatment. Unlike ECT, which is done to the patient, psychedelic psychotherapy is done by the patient. The therapists can create a safe, supportive and insightful environment, but the hard work of acknowledging, accepting and integrating inner emotions and cognitions can only be accomplished by the patient. If a patient cannot fully comprehend that a wide range of powerful emotions can be catalyzed by psychedelic psychotherapy and cannot fully assent to the challenge of experiencing those emotions, the treatment could prove counterproductive. Psychedelic psychotherapy is intended only for patients who can and do voluntarily consent to receive the treatment.

¹⁵³¹These reports were required by Massachusetts Mental Health Regulation 181 (effective May 1, 1973). These regulations do not appear in a search of current Massachusetts State regulations, suggesting that the

specified by the American Psychiatric Association¹⁵³² with detailed reports submitted to the DMH about all treatments that took place from 1977-1980, Drs. Benedict and Saks found that approximately 90% of patients received treatment that was not in accord with at least one aspect of the consensus standards.¹⁵³³ It was apparent from the study that no DMH official monitored the ECT reports that were sent in. As a result, nobody attempted to increase the use of consensus standards. During this same time period in Massachusetts, there seemed to have been virtually no malpractice litigation related to ECT that could have served as a vehicle to draw attention to the consensus standards. The authors reported that, “the great majority of variables that might be expected to have something to do with the likelihood of proper ECT administration were not significantly related to that behavior... Many potential sources of transmission or enforcement of correct treatment practices—professional association membership, training and education, and informal peer review—statistically and sometimes literally had no relationship to compliance with the consensus.”¹⁵³⁴ They found that, “those who reported that they felt that their practice had been informed by the medical literature do in fact tend fairly strongly to behave more in accord with recommended practice.”¹⁵³⁵

Among the most important factors in reducing misuse of any medical intervention are providing the health care providers with adequate training and continuing education combined with a monitoring and feedback loop so that deviations from acceptable practice can be corrected. The study by Drs. Benedict and Saks of the use of ECT in Massachusetts provides evidence that reporting systems without review and feedback are ineffective in regulating professional practice. The authors speculate that both the medical professionals and the public would benefit most from proactive “methods aimed at improving medical practice through education and feedback rather than from methods designed to detect inappropriate treatment which has already occurred.”¹⁵³⁶

Training of ECT Practitioners

In light of the heated controversy over the use of ECT by the psychiatric profession, it would be logical to assume that comprehensive educational programs were offered to

regulation was repealed sometime after 1987, when Drs. Benedict and Saks published their paper.

¹⁵³²American Psychiatric Association, Task Force Report 14: Electroconvulsive Therapy. Washington, DC: American Psychiatric Press, 1978. The APA has since updated its standards for ECT, American Psychiatric Association Task Force on ECT. The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training and Privileging. Washington, DC: American Psychiatric Press, 1990.

¹⁵³³Benedict A and Saks M. The Regulation of Professional Behavior: Electroconvulsive Therapy in Massachusetts. *J Psychiat Law* (Summer 1987): 247-275.

¹⁵³⁴*Ibid.*, 262.

¹⁵³⁵*Ibid.*, 269.

¹⁵³⁶*Ibid.*, 270.

psychiatrists interested in learning how to administer ECT. Such an assumption is, however, incorrect.

In 1986, Dr. Max Fink wrote an editorial stating, “Formal training in ECT is not generally available. Few postgraduate psychiatric training programs include convulsive therapy in the curriculum. Therapists are usually trained by preceptorship, or, from time to time, in 1- or 2-day training sessions designed to meet continuing medical education training credits, organized at meetings of the American Psychiatric Association or in private hospitals. These sessions are in lecture format and, while practical issues are discussed, are poor substitutes for “hands-on” experience... There is a call for the development of certification procedures, with guidelines, training programs, and certification tests. No such programs exist in the U.S. or in some other western countries informally surveyed.”¹⁵³⁷

In 1995, nine years after Dr. Fink’s editorial, another editorial in the same journal but by a different author discussed deficiencies in the training of ECT practitioners. Dr. Martin Klapheke noted, “I am concerned that we lack clear national standards for privileging in ECT. The American Psychiatric Association (APA) Task Force Report on ECT (1990) developed acceptable standards for training in ECT during psychiatric residencies. The Task Force, however, implied that these same criteria are appropriate for granting privileges for the independent practice of ECT, even though the graduating resident may have administered only the minimum 10 ECT under supervision... I am reluctant to certify their competence to independently practice ECT.”¹⁵³⁸ Dr. Klapheke went on to propose three levels of privileging: supervised practice of ECT; independent practice of ECT; and supervisor of the practice of ECT.”¹⁵³⁹ Privileging for the supervised practice of ECT would require didactic instruction amounting to four hours of lectures. Privileging for the independent practice of ECT would require 50 ECT sessions under supervision, in at least ten different patients including some that were high-risk, plus the management of ten patients through pre-ECT examination, ECT sessions and post-ECT period. Privileging for supervisor of the practice of ECT would require administration of 100 ECT sessions in at least 20 patients, some high-risk. Dr. Klapheke concludes by stating, “unless we develop a consensus regarding national standards for privileging in ECT, we are inviting—even provoking—greater government regulation.”¹⁵⁴⁰

In 1996, the Royal College of Psychiatrists conducted an audit of the practice of ECT in England and Wales.¹⁵⁴¹ This was the third in a series of audits, with the first having taken place in 1981 and the second in 1991. The results were disappointing. The auditors

¹⁵³⁷Fink M. Training in Convulsive Therapy. *Convul Ther* 2 (1986) 4:227-228.

¹⁵³⁸Klapheke M. Privileging for ECT. *Convul Ther* 11 (1995) 1:57.

¹⁵³⁹*Ibid.*, 57.

¹⁵⁴⁰*Ibid.*, 58.

¹⁵⁴¹Duffett R, Lelliott P. Auditing electroconvulsive therapy. The third cycle. *Br J Psychiat* 172 (May 1998): 401-5.

concluded, “Although some aspects of ECT administration had improved since the last audit in 1991, overall only one-third of clinics were rated as meeting College standards... Only about one-third of clinics had clear policies to help guide junior doctors to administer ECT effectively... Twenty years of activity by the Royal College of Psychiatrists and three large-scale audits have been associated with only modest improvement in local practice.”¹⁵⁴²

In 1998, Dr. Richard Hermann and associates from the Malcolm Weiner Center for Social Policy, Kennedy School of Government, studied the characteristics of physicians who perform ECT. They concluded, “Improving the quality and consistency of ECT training in medical school, residency, postdoctoral fellowships, and psychiatric board examinations would lead to the development of a broader clinical consensus regarding ECT and could narrow variability in its use.”¹⁵⁴³ Also in 1998, Dr. Carl Salzman editorialized that the lack of research with ECT was causing an “ambivalence among American psychiatrists toward this efficacious and safe treatment.”¹⁵⁴⁴ He explained, “Rigorously designed multisite collaborative studies, using modern research techniques, of ECT’s efficacy and predictors and correlates of response, relapse, and maintenance do not exist.”¹⁵⁴⁵

In 1999, four years after Dr. Klapheke’s editorial, Dr. Barry Kramer published an article in which he also criticized the lack of formalized training for ECT. He observed, “Sixty years after its introduction into psychiatric practice, training in electroconvulsive therapy (ECT) is often minimal and standards are lacking.”¹⁵⁴⁶ Dr. Kramer offered an outline for a six-hour course of instruction. He also quoted a powerful *Lancet* editorial about ECT which warned, “If ECT is ever legislated against or falls into disuse it will not be because it is an ineffective or dangerous treatment; it will be because psychiatrists have failed to supervise or monitor its use adequately.”¹⁵⁴⁷

Regulating ECT: Lessons for the Regulation of Psychedelic Psychotherapy

A succession of the major advocates for ECT are in agreement that the lack of rigorous training programs has had deleterious consequences for the field. Dr. Klapheke’s warning that the failure of professional self-regulation can lead to the imposition of

¹⁵⁴²Ibid., 401.

¹⁵⁴³Hermann R, Ettner S, Dorwart R, Hoover C, Yeung E. Characteristics of Psychiatrists Who Perform ECT. *Am J Psychiat* 155 (July 1998) 7:893. See also Hermann R, Dorwart R, Hoover C, Brody J. Variation in ECT Use in the United States. *Am J Psychiat* 152 (June 1995) 6:869-875; Rosenbach M, Hermann R, Dorwart R. Use of Electroconvulsive Therapy in the Medicare Population Between 1987 and 1992. *Psychiat Serv* 48 (December 1997) 12:1537-1542.

¹⁵⁴⁴Salzman C. ECT, Research, and Professional Ambivalence. *Am J Psychiat* 155 (January 1998) 1:1.

¹⁵⁴⁵Ibid., 1.

¹⁵⁴⁶Kramer B. A Teaching Guide for Electroconvulsive Therapy. *Comp Psychiat* 40 (Sept/Oct 1999) 5:327.

¹⁵⁴⁷Editorial. ECT in Britain: a shameful state of affairs. *Lancet* 2 (1981): 1207-1208.

governmental regulation is a reminder that the approval of psychedelic psychotherapy should be accompanied by the simultaneous development of formal educational and certification programs for treatment providers. For psychedelic psychotherapy to have the best chance of becoming an accepted treatment modality within modern psychiatry, a strong and sustained emphasis must be placed on the development of a comprehensive program of educational certification that is established right from the beginning of the emergence of this treatment.

Regulations in Massachusetts, California and Texas mandated reporting to state health officials of information about all ECT treatments administered within those states. Practitioner compliance with these regulations demonstrated that it is possible in practice to require and obtain the filing of a report about virtually every instance in which a specific psychiatric treatment is delivered. The regulations have also demonstrated that valuable information can be gathered from the review of the reports that are collected.

The lessons for psychedelic psychotherapy from the regulation of ECT are that by building a solid foundation of education, training, continued research, and carefully monitored treatments through a national registry of patients, it may be possible to bring about the eventual acceptance of psychedelic psychotherapy as a legitimate and socially beneficial therapy.

The Design of a Regulatory System for Psychedelic Psychotherapy

The concluding portion of this chapter will offer a series of recommendations for the design of a regulatory system for psychedelic psychotherapy to reduce misuse, abuse, diversion and the negative effects of information about medical use on non-medical use patterns. The recommendations are briefly summarized at the conclusion of the chapter. The actual details of the regulatory system will require taking into account the specific knowledge gained during clinical trials that may lead to the approval of some form of psychedelic psychotherapy. Information gathered from a review of the ongoing regulation of GHB, thalidomide, methadone and electroconvulsive therapy as well as other highly regulated prescription medicines will also be needed. Nevertheless, some general outlines of a regulatory system can be proposed at this time.

The operating principle in these proposed regulations is that the reintroduction of psychedelic psychotherapy into FDA-approved socially sanctioned contexts is a delicate and bold endeavour that should be conducted with substantial and deliberate care. These regulations respond to one aspect of the government's diversion control strategy, which has been described as follows, "Rather than find and punish the small number of wrongdoers, the government's attitude is often to restrict access to the drug and thereby penalize the innocent patient."¹⁵⁴⁸ This reality suggests the importance of prioritizing prevention of

¹⁵⁴⁸Angarola R, Minsk A. Regulation of Psychostimulants: How much is too much? in Schwartz H. (ed.) *Psychiatric Practice Under Fire—The Influence of Government, the Media, and Special Interests on Somatic Therapies*. Washington, DC: American Psychiatric Association Press, 1994: 63-84.

misuse, abuse and diversion, if need be increasing the expense and limiting access to patient care, at least in the initial stages of the introduction of psychedelic psychotherapy into medical practice. This strategy is reinforced by the willingness of FDA to consider the relaxation of initial restrictions and procedures that have proven in practice to be excessive, as is in process with the regulation of thalidomide.¹⁵⁴⁹

Immediate Implementation of Phase IV Studies: A Voluntary Agreement

As this chapter has demonstrated, neither FDA nor DEA can or should limit off-label prescription of approved medications. In view of the extremely wide range of possible therapeutic applications that have been researched or claimed for psychedelic drugs over the decades, the lack of limits on off-label prescriptions could result in such widespread experimentation that it could be difficult to control misuse, abuse and diversion. From a strategic perspective, the sponsor and the FDA may find common ground in a mutual agreement to make NDA approval contingent upon the implementation of a large-scale Phase IV study in one or two thousand patients with the approved clinical indication, requiring at least several years to complete.¹⁵⁵⁰ According to FDA regulations, Phase IV studies could include studies in which a different dose or dosing schedule was being tested.¹⁵⁵¹ The primary advantage to the sponsor of conducting a Phase IV study is that patient treatments could proceed anywhere in the country under the authorization of an FDA IND.¹⁵⁵²

¹⁵⁴⁹personal communication, Ken Restack, June 8, 2000.

¹⁵⁵⁰21 CFR Sec. 310.303 Continuation of long-term studies, records, and reports on certain drugs for which new drug applications have been approved.

¹⁵⁵¹21 CFR 312.85 Phase 4 studies. Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain postmarketing (phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.

¹⁵⁵²FDA does not often give INDs for approved drugs. Yet Mr. Mike Klein, FDA Controlled Substances Staff, was of the opinion that some sort of arrangement would be possible to permit post-approval treatments to take place under the auspices of the FDA while state rescheduling efforts were taking place. He explained, "There are circumstances in which an IND is needed for an approved drug product and is certainly recommended. When the information that is going to be sought from a clinical study is likely to present new safety concerns, such as, in a new at-risk population, or when an approved drug is being developed for a new therapeutic indication, an IND is needed. The safety profile and risk of exposure in these different groups is not the same. Other circumstances where an IND is needed is when the information being sought will be used to promote, advertise or market the drug, or will be incorporated into the product labeling." personal communications, Mr. Mike Klein, June 1, 2000 and June 8, 2000. If the clinical trials conducted for MDMA in the treatment of PTSD administered only one or two doses to the patients, a reasonable case could be made that the risks and benefits of administering several additional

Without such FDA approval, no treatments could take place in any state until the state legislature had passed a special bill rescheduling the psychedelic drug to permit its medical use. Trying to have such bills passed is likely to be a lengthy and exhausting process.¹⁵⁵³ The primary advantages of a Phase IV study to the FDA is that the sponsor would be able to meet patient needs more quickly and would be focused on implementing a study in which the only treatment that would be permitted would be in the approved patient population.

Conducting a large Phase IV study immediately after FDA approval would also facilitate the efforts of the initial core group of researchers to teach their therapeutic techniques to new practitioners. A clinical research setting would provide the most controlled context within which to train new treatment providers. In a Phase IV study conducted under an IND, the delivery of the therapy would need to be monitored to ensure compliance with a treatment manual. A Phase IV study would incorporate individual training and monitoring of all new treatment providers, with evaluation and feedback loops permitting standards of care to be maintained.

During the conduct of the Phase IV trial, the sponsor would be able to work gradually on a state by state basis to have the approved drug rescheduled so that it could eventually be prescribed independent of a Phase IV study. The sponsor's lobbying effort could be conducted with the assistance of local patients and treatment providers involved in the Phase IV study. Research could also be initiated during this period into the treatment of additional patient populations under the auspices of new FDA-approved IND protocols.

The Phase IV study will be conducted under a carefully designed and monitored protocol. The regulations that follow are designed for the eventual administration of MDMA outside of the Phase IV study.

Training of Treatment Providers: Who Can Administer Psychedelic Psychotherapy?

What limits if any should be placed on which treatment professionals will be permitted to assume primary responsibility for the administration of psychedelic psychotherapy, initially in the context of the Phase IV study and ultimately beyond? When FDA approves a drug for prescription use, any physician is legally permitted to prescribe that drug for any indication.¹⁵⁵⁴ For example, internists frequently prescribe psychiatric treatment episodes per patient drug were still unknown and should be studied in the context of a new IND.¹⁵⁵³ Congress did place the medical use of GHB in Schedule III when it placed its non-medical use in Schedule I, thus expediting state action to approve its medical use. Similar bifurcated scheduling by Congress is not likely for any of the classic psychedelics or MDMA. The later drugs are already in Schedule I and thus do not require the attention of Congress, unlike GHB, which had previously been unscheduled. In addition, the medical uses of the classic psychedelics or MDMA will be more controversial politically, since the therapeutic mechanism of action of the classic psychedelics and MDMA, when used as adjuncts to psychotherapy, is directly related to their psychedelic effects, unlike GHB, which has a therapeutic effect on sleep patterns through the use of non-psychedelic doses.

medications such as Prozac even though they have not received training in psychiatry in medical school or in a psychiatric residency.¹⁵⁵⁵ However, psychedelic drugs as adjuncts to psychotherapy are unlike standard medical treatments, since their healing potential depends more on the context in which they are administered and on the psychotherapeutic skill of the prescriber than on the mere fact that they are administered. If any physician, regardless of training in the management of psychological processes, were able to prescribe a newly approved psychedelic drug, potentially tragic cases of misuse and abuse would be more likely than if prescribing practices were limited to some class of prescribers with specialized training.

Two different sets of skills are required of the prescriber in order to assure that psychedelic psychotherapy is administered safely and effectively. First, the prescriber should be able to evaluate the physical risks that the patient may be exposed to during the course of therapy and determine whether these risks can be managed. In general, the principal physical risks that psychedelics can pose are an increased heart rate and blood pressure and a slight possibility of triggering a seizure in seizure-prone patients. Physicians of any specialty should be qualified to assess these physiological risks. Though heatedly debated, perhaps specially trained and tested clinical psychologists, social workers and other psychotherapists could also assess these risks.¹⁵⁵⁶ Second, the prescriber needs to manage psychological risks and assess the psychological character of the patient. Psychedelic psychotherapy, with any of the classic psychedelics or even with MDMA, can bring unconscious conflicts to the surface and can leave patients worse off unless these experiences are handled skillfully. While it is true that the biological orientation of modern psychiatry leaves many psychiatrists ill-trained in verbal psychotherapy, psychiatrists more than any other medical specialists are trained in diagnosing and treating the full range of mental conditions.

Rather than restricting use to a preexisting class of physicians, a specially-designed performance test of sorts might be developed that could be open to all physicians, perhaps to all licensed psychologists and therapists and maybe even to religious professionals or other people licensed in the healing or counseling professions. In their detailed examination of whether prescribing privileges for a limited class of psychoactive drugs should be extended to clinical psychologists with additional training in pharmacology, Phyllis Coleman, J.D.

¹⁵⁵⁴37 FR 16503 (August 15, 1972) Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration; Notice of Proposed Rule Making.” Once the new drug is in a local pharmacy after interstate shipment, the physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the Food and Drug Administration.”

¹⁵⁵⁵Kramer P. *Listening to Prozac*. New York: Penguin, 1997.

¹⁵⁵⁶Coleman P, Shellow R. Prescribing privileges for psychologists: Should only “Medicine Men” control the medicine cabinet. *J Psychiat Law* (Fall/Winter, 1990): 269-318.

and Dr. Ronald Shellow conclude, “Based on training and intellectual orientation, psychologists and other nonphysician professionals are simply not prepared to prescribe medicine.”¹⁵⁵⁷ ¹⁵⁵⁸ In addition, State laws sometimes preclude psychologists from administering a drug to a patient. For example, California’s Business and Professions Code states, “The practice of psychology shall not include prescribing drugs, performing surgery, or administering electroconvulsive therapy.”¹⁵⁵⁹

Even if a performance test were limited only to physicians, psychiatrists more than any other speciality would come to the test with substantially more training and practical experience than other physicians in the management of the types of psychological phenomena that psychedelic psychotherapy can generate. Due in part to the complexity of designing and implementing an effective test, this option is not recommended for the initial introduction of psychedelic psychotherapy into medical practice. Another consideration is that the initial practitioners of such a controversial new practice as psychedelic psychotherapy should be as socially sanctioned as possible, with psychiatrists bringing the most credibility to the table.

For an added margin of safety with psychedelic psychotherapy, only board-certified psychiatrists with prior training in the diagnosis and treatment of mental disorders (and special training in the delivery of psychedelic psychotherapy, to be discussed in more detail below) should be allowed to be the treatment professionals with primary responsibility for the delivery of psychedelic psychotherapy. Psychiatrists should have primary responsibility for initial diagnosis, review of patient risk factors, the decision whether or not to treat each individual patient, and the actual writing of each prescription. These restrictions can be enforced by the sponsor through the mail-order distribution system, to be discussed later in this chapter.

Unfortunately, granting monopoly privileges to any class of treatment professionals can result in self-serving abuse of those privileges. If clinical psychologists ever do obtain permission from state regulatory agencies to prescribe a limited class of psychoactive drugs,

¹⁵⁵⁷Ibid., 269.

¹⁵⁵⁸ However, some limited prescribing authority has already been given in some states to ob/gyn practitioners, pediatric nurse practitioners, psychiatric nurse practitioners, optometrists, naturopathic doctors, physician assistants, advanced registered nurse practitioners, clinical nurse specialists, nurse midwives, midwives, nurse practitioners, and doctors of homeopathy. Restrictions include dispensing from a limited formulary (doctors of homeopathy), restrictions based on National Speciality Scope of practice (clinical nurse specialist and pediatric nurse specialist), dispensing only in accordance with Pharmacy Board rules via a signed dispensing procedure and under the authority of a job description (PAs) or a nurse protocol (psychiatric nurse practitioner) and the like. In addition to medical doctors, full prescribing authority has been given in most states to doctors of osteopathy, dentists, veterinarians, and podiatrists. Survey of Pharmacy Law, 1999-2000. Chapter XXV. Dispensing Authority. Park Ridge, IL: National Association of Boards of Pharmacy, 1999: 70-73.

¹⁵⁵⁹Cal Bus & Prof Code § 2904 (2000).

the primary responsibility for psychedelic psychotherapy that this chapter recommends be restricted to psychiatrists should be expanded to include clinical psychologists. If approved, the prescribing practices of psychologists should be closely monitored to determine whether they are in fact able to identify patients with risk factors that would make psychedelic psychotherapy contraindicated.

An important distinction can and should be made between permitting only psychiatrists to assume primary responsibility for patient treatment and the prescription of psychedelics, and permitting treatment professionals with other qualifications to be involved in treatment care as part of the treatment team. Clinical psychologists and other professionals trained and licensed to provide psychotherapeutic services can be as effective as psychiatrists in providing psychotherapeutic guidance during a psychedelic session. Therefore, entrance into the special training and certification program for psychedelic psychotherapy, to be directed by the sponsor, should not be limited just to psychiatrists, but should be open to all treatment professionals trained and licensed by their state to provide psychotherapeutic or counselling services. The prescribing psychiatrist will nevertheless retain responsibility for ensuring that the prescription is administered in a manner that meets professional standards, and thus would be held responsible in cases of malpractice. The prescribing psychiatrist would need to approve all treatment professionals who would work under his or her authorization.

If a treatment facility is large enough to require a director, that director need not be a psychiatrist. As was seen in the studies linking favorable outcomes of methadone maintenance patients with “greater director involvement in patient care and more experience [of the director],” the director of a clinic can have a substantial impact on treatment outcome. Yet there seems nothing inherent in the role of director that requires a medical degree. A strong case could be made that training in clinical psychology would better prepare someone to be a director of a psychedelic psychotherapy treatment center than the neurobiological training that most psychiatrists currently receive. As long as there is a psychiatrist in charge of all diagnoses, decisions to treat, and prescribing, the position of director need not also be a psychiatrist. For an interesting parallel, FDA does not require that the principal investigator on an IND evaluating the safety and efficacy of a new drug be a physician.¹⁵⁶⁰ Still, FDA must be satisfied that all medical aspects of the protocol, such as the medical examination, prescribing, and medical procedures that may be conducted during the experimental sessions, are being adequately attended to.

Training of Treatment Providers: Special Education Requirements

A special education requirement for psychedelic psychotherapy treatment providers will ensure a minimum level of training and expertise. Some of the virtues of a performance test, such as the individualized grading and evaluation, can be incorporated into this special

¹⁵⁶⁰Cocchetto D, Wallace J. Qualifications of investigators for clinical investigations conducted under an IND: A discussion paper. *Drug Info J* 26 (1992) 167-173.

training program. The responsibility for providing this special education lies with the sponsoring organization that obtains FDA-approval for psychedelic psychotherapy. From a legal liability perspective, the sponsor must design a training program that provides the psychiatrist, who has primary responsibility for the prescription, with sufficient information about the proper use of the psychedelic drug. Then, “by providing adequate warnings about drugs to prescribing physicians—those best able to understand and assess risks, and explain options and consequences to patients—companies successfully insulate themselves from malpractice liability.”¹⁵⁶¹

If the FDA approves one form of psychedelic psychotherapy, it will only be after safety and efficacy have been demonstrated, probably in two large multi-site studies in which at least 300 people will have received the test drug at least once and perhaps several times. The sponsor would probably have available several experienced therapeutic teams who could direct the training program. They could serve as core teachers to others interested in learning how to administer psychedelic psychotherapy to their patients. The sponsor would also have a written, well-tested treatment manual describing the key elements of the entire treatment process. The manual would contain details for conducting the psychedelic sessions as well as the non-drug psychotherapy sessions for preparation and integration.

The core group of initial researchers/teachers along with the treatment manual would become the basis of the educational seminars that the sponsor would offer to train and certify future practitioners. The sponsor could charge the trainees a fee for the training or could offer the training for free. Though the design and depth of these educational seminars will need to be responsive to the specific form of psychedelic psychotherapy approved, a crude outline can be proposed. These seminars should be substantially longer than one weekend in length. The first seminar should last at least a week or more. It should be followed by a period of several weeks or months for reflection, integration and reading of assigned materials. The program could conclude with a final training session lasting another week or more. The training should include supervised treatment sessions, at least two in which the trainee is acting as an assistant to an experienced teacher who is working with a patient, and another two in which the trainee assumes primary responsibility for patient care under the direct supervision of a more experienced teacher. Eventually, there could be different levels of training for the different people involved in a treatment facility such as the director, the primary therapists, and support staff. There should be continuing education requirements in order to keep the certification active.

Should Trainees be Required to Have a Self-Experience?

One perennial issue in the field of psychedelic psychotherapy is whether therapists interested in administering psychedelics to patients should be required to participate in at least one training session in which they self-administer a psychedelic drug. The collective wisdom of virtually all psychedelic therapists is that this sort of self-experience is

¹⁵⁶¹Coleman, Shellow (1990): 293.

necessary.¹⁵⁶² It provides a degree of insight and requires an element of courage, both of which contribute to increasing the therapist's subsequent effectiveness in assisting patients as they navigate through difficult inner landscapes while under the influence of a psychedelic drug. Nevertheless, despite the genuine benefits of personal experience, it is still entirely possible that a talented therapist without such experiences could effectively assist patients who are undergoing psychedelic psychotherapy. Furthermore, there is something deeply troublesome about requiring a trainee to have a drug experience that should be totally voluntary. Requiring a personal experience might also drive skeptical or cautious people away from the training program, at a time when such people could provide important checks and balances to the enthusiasms of the newly forming treatment specialty.

Rather than requiring that all trainees have a personal experience with the approved psychedelic drug, a graduated license should be created, with a basic version for those who choose not to self-administer the drug and a basic plus version for those who do choose to do so. Each license should have identical prescribing privileges. Some patients may prefer to be treated by therapists who have had their own experiences, while other patients may not have a preference. Over time, the monitoring of treatment outcomes through the patient registry system (to be discussed below) will permit a quantitative analysis to be conducted to determine whether practitioners who have had their own psychedelic experiences are more effective therapists than practitioners who choose not to have such experiences.

In practice, it is likely that the vast majority all people who seek training in psychedelic psychotherapy will choose to have a self-experience session at some point during the training program. From a regulatory perspective, these training sessions should be part of a special IND that permits the gathering of data on the use of the approved drug in "healthy" trainees. It would be difficult to consider these training sessions as legal off-label prescriptions, since no psychiatric condition is being treated.

Minimum Requirements for the Location of Psychedelic Psychotherapy

One basic regulatory decision is whether psychedelic psychotherapy should be restricted to use in a hospital, to a dedicated treatment facility like a methadone clinic, or to multi-purpose facilities that meet certain minimum standards. Another option is to make no restrictions on location, with treatment providers authorized to administer psychedelic psychotherapy anywhere of their choosing. The decision on location is dependent in large part on the characteristics of the treatment session itself. It will be assumed that psychedelic psychotherapy is delivered to one patient at a time in individual sessions. Though group sessions can also be therapeutic, the initial clinical trials with psychedelic psychotherapy are likely to involve individualized treatment, as will the subsequent Phase IV trials. Even with individual treatment sessions, pre-treatment preparation sessions and post-treatment

¹⁵⁶²Masters R, Houston J. *Varieties of Psychedelic Experience*. New York: Dell, 1966: 131. The authors outline the training of the guide, stating as a requirement that, "the guide has experienced the drugs and so is able to understand the experience of the subject."

integrative sessions can be organized on a group basis if the treatment professionals choose to do so.

Characteristics of the Treatment Session

For the classic psychedelics such as LSD, psilocybin, mescaline and ibogaine, the treatment session is likely to last 6-10 hours. Sessions with MDMA are usually shorter, lasting 4-6 hours. Sessions with DMT or ketamine can last only an hour or two. In patient populations, the sessions are likely to involve the emergence of difficult emotional material that can prolong the length of the session and require post-session reflection and integration to maximize therapeutic outcome.

Ideally, the treatment should take place in a private room with attached bathroom. Patients should not have to enter any public spaces to reach a bathroom. With the maximum amount of privacy, patients will be able to focus their energies inwards. The treatment room should be sufficiently insulated from distracting noises from outside and should permit patients the freedom to make noises associated with emotional release such as moaning, crying and yelling. Prerecorded music should be available as an option during the treatment session to facilitate emotional release.¹⁵⁶³

In order to maximize the therapeutic potential of the treatment session, to allow sufficient time for follow-up and integration in a private and protected environment, and to ensure that patients return to their homes thoroughly grounded, patients receiving any of the long-lasting psychedelics as well as MDMA should be required to spend the night in the treatment facility. Some psychedelic psychotherapy sessions can last quite a long time and leave the patient exhausted, physically and emotionally. The treatment facility should therefore be furnished so that the patient could spend the night comfortably in the treatment room, or in a room nearby. Visits from significant others near the end of the treatment session can often deepen and clarify emotions and insights that the patients have been wrestling with. These contacts also provide a way to channel the energy of the patients' treatment sessions back into their daily lives. The treatment room should permit at least one family member or close friend the ability to stay the night as well.

Minimum Requirements for Treatment Facilities

Requiring that psychedelic psychotherapy take place only in a hospital setting will impose substantial financial costs. The only justification for requiring that psychedelic psychotherapy be limited to hospitals is enhanced safety for the patients. The medical emergencies that can conceivably occur during a psychedelic session that might be treated most effectively in a hospital are heart attack and stroke. Seizures, though also possible during a psychedelic session, are short-lived, rarely result in any significant long-lasting injury, and almost never require hospital treatment.

Psychotic reactions to psychedelic psychotherapy are also possible. Such reactions

¹⁵⁶³For a discussion about the role of music in psychedelic psychotherapy, see Bonny H, Savary L. *Music and Your Mind—Listening with a New Consciousness*. New York: Harper and Row, 1973.

can for the most part be treated as easily outside a hospital as inside. The management in patient populations of difficult emotional experiences is generally handled by therapists through verbal reassurance and encouragement to patients to move through their emotions rather than trying to stop any emergent psychological processes. As a last resort, additional medication such as tranquilizers can be administered. The only advantage of a hospital location is that patients with a violent psychotic reaction who could not be handled by their therapists could be more rapidly subdued by hospital staff, who would probably show up sooner than would emergency medical personnel.

The historical record of psychedelic research^{1564 1565} indicates that these adverse outcomes are so rare as to make the restriction of psychedelic psychotherapy to hospitals unnecessary and excessive. After reviewing the number of adverse effects in about 5000 patients who had taken LSD or mescaline more than a total of 25,000 times, Dr. Sidney Cohen concluded, “reports of untoward events occurring in connection with the experimental or therapeutic use of the hallucinogens have been surprisingly infrequent.”¹⁵⁶⁶ The Harvard psilocybin research project, in which none of the experimental sessions took place in a hospital, reported a reassuring degree of safety, with the absence of any heart attacks, strokes or violent psychotic reactions.¹⁵⁶⁷

Due to the virtual absence of heart attacks, strokes and violent psychotic reactions during psychedelic sessions, no specialized medical equipment, such as a medical crash cart, need be required in the treatment facility. Requiring prior screening of psychedelic psychotherapy patients by a licensed physician to determine whether patients have any risk factors for heart attack, stroke or violent psychotic reaction that would make psychedelic psychotherapy contraindicated is a sufficient precaution against these adverse events.

Requiring that treatment be restricted to specialized treatment facilities offers several advantages. Dedicated facilities will likely incorporate physical features that will maximize the effectiveness of the psychedelic psychotherapy. The costs involved in creating such treatment facilities will likely limit their number, making them easily monitored by regulatory agencies. However, dedicated facilities such as methadone clinics require a large number of patients to sustain themselves financially. While it is possible and even desirable that certain treatment providers will develop a specialty in the provision of psychedelic psychotherapy, the practice of psychedelic psychotherapy is likely to develop gradually and initially be focused primarily on patients with the approved clinical indication. Requiring that

¹⁵⁶⁴Strassman R. Adverse reactions to psychedelic drugs: A review of the literature. *J Nerv Ment Dis* 172 (1984) 10:577-95.

¹⁵⁶⁵Cohen S. Lysergic acid diethylamide: side effects and complications. *J.Nerv Ment.Dis* 130 (1960): 30-40.

¹⁵⁶⁶Ibid.

¹⁵⁶⁷Leary T, Litwin G, Metzner R. Reactions to psilocybin in a supportive environment. *J Nerv Ment Dis* 137 (1963): 561-573.

psychedelic psychotherapy take place within a dedicated facility will impose too large a financial burden on the treatment providers and their patients.

A middle ground between dedicated treatment facilities and no regulations on facilities is to require licenses and minimum standards for treatment facilities in which psychedelic psychotherapy will take place, but permit the facilities to serve multiple purposes. Dedicated treatment facilities may develop, but they would not be mandated. The requirement of certain minimum standards will help facilitate patient care, and the requirement for licensing of facilities will assist regulators in monitoring the facilities and treatments. This is the recommended regulatory option.

Patients may face increased monetary costs in terms of higher fees and longer travel times if psychedelic psychotherapy is required to be delivered only in sponsor-licensed facilities that meet certain minimum standards. These costs do not outweigh the value of the additional safety, comfort and therapeutic context provided by facilities that meet these standards. The social controversy over the medical use of psychedelics argues for a regulatory system that emphasizes the elimination to the extent possible of potential adverse effects resulting from substandard treatment. It therefore seems wise to restrict psychedelic psychotherapy to locations that meet certain minimum standards. In practice, it should be possible to meet the minimum standards for facilities in some private offices that have the requisite features. Therapists may not want to remodel their offices into a dedicated single-use facility for delivery of psychedelic psychotherapy, nor should they be required to do so.

These facilities should be inspected and licensed by the sponsor, at least in the first phases of the implementation and integration of psychedelic psychotherapy into medical practice. Licensing facilities could also be a matter for state regulatory agencies, or even the FDA, though staff time for this purpose may be unavailable. The incentives of the sponsor to enforce the minimum standards are mixed. More treatments result in more income. However, substandard treatments could result in a backlash, trigger lawsuits, hinder rescheduling on the state level, or even result in the withdrawal of FDA approval for the drug treatment.¹⁵⁶⁸ On balance, the incentives of the sponsor are to emphasize long-term

¹⁵⁶⁸For example, Janssen Pharmaceutical announced on March 23, 2000 that as of July 14, 2000 it would cease marketing Propulsid (cisapride) Tablets and Suspension, for the treatment of Gastroesophageal reflux disease (GERD) and several other indications. Propulsid had been associated with an unacceptably high incidence of serious cardiac arrhythmias and deaths that were not reduced even after labeling changes and educational programs offered by the sponsor. After July 14, 2000, Propulsid will be available only to patients who had failed on all available alternative treatments, only within the context of an FDA-approved IND that had also been approved by an IRB, and then only to patients with a limited set of indications. Prescribing physicians were limited to those who were board-certified in a few limited medical specialties. FDA Talk Paper T00-14, Janssen Pharmaceutical Stops Marketing Cisapride in the US. March 23, 2000 <http://www.fda.gov/bbs/topics/ANSWERS/ANS01007.html>, FDA Medwatch "Dear Healthcare Provider" Letter, Propulsid Tablets and suspension, Jansen Pharmaceutical, April 12, 2000. <http://www.fda.gov/medwatch/safety/2000/propull1.htm>

consequences and implement its licensing and training responsibilities in a diligent and serious manner.

No Restrictions on Facilities

The least restrictive regulatory approach would be to have no requirements for the facility, leaving the choice of treatment location entirely up to the treatment provider. However, since off-label prescriptions cannot be restricted, there is the possibility of significant amounts of misuse and diversion, along with appropriate medical use. The absence of limits on the location of treatment could result in the use of psychedelic psychotherapy for a variety of indications in public settings, though probably relatively quiet locations. This situation could seem close to legalization to unsympathetic observers, even though rational arguments can be made for the therapeutic utility of administering psychedelic psychotherapy in natural settings. As Dr. Horgan and associates have observed, misuse and diversion are interrelated categories. They comment, “Sometimes the difference between drug diversion, which is the focus of law enforcement, and drug therapy, which is in the realm of health professionals, is fundamentally related to standards of care accepted in the medical community. Systematic attention to prescribing and diversion patterns for controlled substances could heighten collective and individual awareness among practitioners regarding the proper use of those drugs.”¹⁵⁶⁹

If no licenses were required for the facility, enforcement authorities would not be able to identify treatment locations and would have a much more difficult time monitoring treatments. Although regulations governing the training and licensing of treatment professionals, with monitoring of their prescribing practices, are more important than controls over the location of treatments, the latter is also an important regulatory instrument. In view of the need to integrate psychedelic psychotherapy carefully and slowly into accepted medical practice, the no-restrictions option should be rejected.

Staffing Requirements

Psychedelic psychotherapy treatment sessions can last six to eight hours, sometimes even longer. As a result, the therapist will probably need at some point in time to leave the treatment room for food, to go to the bathroom, or just to take a break. In order to maximize the therapeutic environment and minimize the possibility of panic reactions, at no time should a patient in an altered state of consciousness be left alone in the treatment room, even if it seems that the patient is not working through difficult emotions at that moment. Therefore, it should be required for there to be at least two treatment professionals in the treatment facility, though not necessarily in each treatment room, during all active portions

¹⁵⁶⁹Horgan C, Prottas J, Tompkins C, Wastila L, Bowden M. A Research Agenda for Prescription Drug Diversion Control. in (eds.) Cooper J, Czechowicz D, Molinari S. *Impact of Prescription Drug Diversion Control Systems on Medical Practice and Patient Care*. Washington, DC: NIDA Research Monograph Series #131. Washington, DC, NIH Publication #93-3507. 1992: 311.

of a treatment session, defined as the period after the administration of the dose, after the peak of the experience, and close but not exactly back to baseline. This requirement will ensure that if one therapist leaves the treatment room for personal reasons, another treatment professional can remain with the patient. One of the treatment professionals can be in training and not yet specially certified by the sponsor or licensed by the state, reducing the salary costs if both treatment professionals were required to be licensed. Requiring the presence of two treatment professionals in the facility also makes patient management easier in the unlikely event of a temporary psychotic reaction or medical emergency. While this regulation will increase the cost of the treatment, it will add a margin of safety and also provides an opportunity for the training of additional treatment professionals.

Though extremely rare, there have been incidents in which a psychiatrist delivering psychedelic psychotherapy sexually abused several patients. The loving and trusting feelings that can be induced by MDMA can make patients more vulnerable to sexual pressure. One method of reducing the opportunities for sexual abuse is to require that therapists work in teams, with two treatment professionals required to be present in the room with the patient during the active phase of the treatment session. The presence of a female nurse when gynecological and obstetrical examinations are to be conducted by a male physician is a response to a somewhat similar concern,¹⁵⁷⁰ though the duration of the exam and the double-staffing takes only a matter of minutes as opposed to the multiple hours of a psychedelic session. Requiring two treatment professionals in the treatment room with a patient during the active phase of the treatment session would substantially increase the cost of the treatment. A less expensive regulation is simply to require two treatment professionals present in the treatment facility when psychedelic psychotherapy is administered, permitting one of the treatment professionals to be working with other patients or on other matters. While this is less than a perfect solution to the potential problem of sexual abuse, it balances risk reduction with cost. If there are two patients being treated, three treatment professionals will be required so that one therapist can take a break and still leave someone with each patient.

An additional safeguard could be a requirement that all treatment sessions be videotaped. However, such a system could make some patients uncomfortable. It also raises issues of the storage and handling the tapes, as well as the possible need for cameras in multiple locations of the treatment facility including bathrooms. Unless a need for such monitoring becomes evident, it need not be required.

Many psychedelic therapists prefer a male/female co-therapist team, under the rationale that this provides the patient with the best opportunity to catalyze emotions and issues that have to do with their relationships with members of either sex. However, requiring male/female co-therapist teams would be a burdensome inconvenience in terms of scheduling and should not be required.

¹⁵⁷⁰This response is not required by regulatory agencies but is a practice recommended by insurance companies seeking to avoid the costs of possible lawsuits.

Since patients will be required to spend the night in the treatment facility, overnight staffing is another issue to consider. Patients who have just experienced a powerful psychedelic experience should not remain overnight in the facility by themselves. If a family member or friend decides to join the patient, a member of the treatment staff should still remain in the facility overnight. The person fulfilling this function need not be a licensed therapist. This job can be filled by a student, intern, or anyone else capable of taking care of the physical safety of the patient in case of fire or other emergency or responding to requests from the patient for food, assistance in going to the bathroom or other similar sorts of non-medical, non-therapeutic services. One of the treatment professionals will be on-call throughout the night and all the next day. This requirement for overnight stay makes the facility resemble an in-patient treatment facility more so than a physician's office for out-patient care.

A post-session follow-up interview with at least one of the treatment professionals should be scheduled for the morning after the session. After the follow-up interview, the patient can depart for home when both treatment staff and patient agree that it is safe for the patient to do so.

Distributing the Drug Only Through the Mail

The system of distributing the drug only through the mail offers numerous advantages to control misuse, abuse and diversion.¹⁵⁷¹ The sponsor or a third party that directs the distribution and patient registry can ensure that only trained and certified practitioners will have access to the drug by shipping only to people on the list of trained and certified practitioners. Distribution through the mail enables the sponsor, independently or through a third party, to establish and maintain a direct channel of communication with all the psychiatrists who will be prescribing psychedelic psychotherapy to their patients. The sponsor or third party is in an excellent position to collect reports about all treatment sessions for research, monitoring and feedback purposes. If reports are late, additional supplies can be placed on hold.

Distribution by mail also saves the sponsor the substantial amount of money that would have been needed to stock pharmacies. There are about 63,000 retail pharmacies in the United States. Supplying them all or even a small fraction of them would result in over manufacturing and over distributing.¹⁵⁷² By removing the drug from all pharmacies, one possible spot for diversion has also been avoided. While it is possible that some shipments may get lost in the mail, packages can fairly easily be traced. The total quantity of drug in each package sent to a physician can be limited to a one, two, or three week supply, reducing the amount that would be lost or stolen if a package is lost in the mail.

¹⁵⁷¹A similar proposal has been made for the distribution of marijuana for medical purposes, though in this case the proposal is to mail the marijuana directly to the patients rather than the doctors. Hollister L. Commentary: An Approach to the Medical Marijuana Controversy. *Drug Alcoh Depend* 58 (2000) 6.

¹⁵⁷²personal communication, Ms.Patti Engel, March 29, 2000.

Distribution by mail does not directly address the issue of diversion by the physician, for personal use or personal profit. Among medical specialties, psychiatrists are a relatively high risk group. Self-reported substance abuse and dependence are at the highest levels among psychiatrists and emergency physicians, and lowest among surgeons.¹⁵⁷³ Emergency medicine and psychiatry residents show higher rates of substance use than residents in other specialties.¹⁵⁷⁴ Distribution by mail, with all shipments kept in a central data base, permits the easy identification of those psychiatrists who are ordering well over average amounts, with some level triggering an inquiry by the sponsor. Diversion by physicians can be made somewhat more difficult by requiring a patient registry and the filing of reports on each treatment session, though no system is entirely foolproof.

100% Patient Registry

A reporting system that gathers information on every psychedelic psychotherapy patient and every treatment session should be implemented, similar to data being gathered about thalidomide and ECT in some states, and as will be collected if and when GHB becomes FDA-approved. This system would be designed to monitor the delivery of a new and controversial treatment as it moves from use in the highly controlled clinical research context to the less controlled use in the practice of medicine. The relative transparency of prescribing practices to the sponsor as well as the FDA and the DEA permitted by such a system can have a powerful impact in reducing inappropriate prescriptions, in a manner similar to the triplicate prescription systems used in some states for the prescription of controlled substances. Unfortunately, it is likely that the reporting system will also have a chilling effect to some degree on appropriate prescriptions.¹⁵⁷⁵ This tradeoff seems worth accepting in order to facilitate the approval and acceptance of a controversial treatment.

A concern expressed by Dr. Allen, AMA's Vice-President for Science and Technology, in response to the patient registry required by the thalidomide regulations, was that even writing a diagnosis on the patient record could be an invasion of doctor/patient confidentiality.¹⁵⁷⁶ This issue needs to be looked at carefully. The most useful patient registry would require information on diagnosis, both to track the extent of off-label prescriptions and to gather data on treatment outcomes for patients with a variety of clinical

¹⁵⁷³Hughes P, Storr C, Brandenburg N, Baldwin D, Anthony J, Sheehan D. Physician substance use by medical specialty. *J Addict Dis* 18 (1999) 2:23-37.

¹⁵⁷⁴Hughes P, Baldwin D, Sheehan D, Conard S, Storr C. Resident physician substance use, by specialty. *Am J Psychiat* 149 (Oct 1992) 10:1348-54.

¹⁵⁷⁵Weintraub M, Singh S, Byrne L, Maharaj K, Guttmacher L. Consequences of the 1989 New York State Triplicate Benzodiazepine Prescription Regulations, in (eds.) Cooper J, Czechowicz D, Molinari S. *Impact of Prescription Drug Diversion Control Systems on Medical Practice and Patient Care*. Washington, DC: NIDA Research Monograph Series #131. NIH Publication #93-3507, 1992: 279-293.

¹⁵⁷⁶Thalidomide—Potential Benefits and Risks. An Open Public Scientific Workshop Sept 9-10, 1997. Executive Summary. <http://www.fda.gov/oashi/aids/thalexe.html>

indications. In their review of drug diversion procedures, Dr. Horgan and associates comment, “A diversion control system may generate, organize, centralize, or otherwise facilitate access to data that threaten the confidentiality of physician-patient relationships. Interviews carried out in this study strongly suggested that confidential and sensitive information was closely protected.”¹⁵⁷⁷ There will be ample time to evaluate the integrity of the patient registration systems for GHB and thalidomide prior to the need to implement such a system for psychedelic psychotherapy. Appropriate protections may need to be put in place or strengthened.

The sponsoring organization or perhaps more appropriately a third party paid by the sponsor but organizationally independent of it, rather than state or federal health officials, would be responsible for collecting and evaluating the data. Data would be made available to governmental agencies upon request, or through shared real-time access to the data base. For GHB, Orphan Medical is considering having its pharmaceutical distributor establish and manage the patient registry, with patient information kept confidential and not shared with the company.¹⁵⁷⁸ DEA, FDA and State Medical Boards will have the authority to review the patient registry at any time.¹⁵⁷⁹

The reporting of data should be the responsibility of each patient’s primary therapist. The patient will also be requested to submit a brief self-report form one week after treatment and a brief self-report follow-up form three months after treatment. Depending on the level of detail required to be submitted, it could become possible to use the system to determine the exact number of prescriptions for the approved indication and for each off-label indication, with this information linked to the DEA for purposes of determining annual production quotas. It could also become possible to gather detailed patient demographic information linked to treatments delivered and subsequent therapeutic outcomes, analyzed in general and by specific treatment provider, with data on the incidence of adverse effects within different subgroups of patients. Longer-term follow-up studies could also be conducted. Data from the patient registry on off-label prescriptions could also guide the selection of additional patient populations for further controlled clinical testing.

The patient registry also permits the sponsor to impose and enforce limits on the frequency and total consumption of the drug that any individual patient can consume, if such limits are considered desirable either by the sponsor or by FDA. For example, patients could be limited to two psychedelic sessions in any month and a total of eight sessions per year. These limits will vary depending on the drug as well as the patient population. Limits could respond to issues of toxicity and the likely depth of the experience and consequent need to provide adequate time for the patient to process and integrate the material. These sorts of

¹⁵⁷⁷Horgan et al. (1992): 312.

¹⁵⁷⁸personal communication, Dr. Dayton Reardan, June 7, 2000. Dr. Reardon is Vice President of Regulatory Affairs, Orphan Medical.

¹⁵⁷⁹personal communication, Dr. Dayton Reardan, June 7, 2000.

clinical issues might best be left for the treating psychiatrist to decide, but could be arbitrarily determined by regulation. Patient age limits as well as other inclusion or exclusion criteria could also be imposed and enforced through the use of the patient registry, depending on whether patient information was required prior to shipping the drug or whether reports were submitted after treatment had taken place.

Limits on Advertising

The sponsor should voluntarily offer to refrain from placing ads aimed at the general public in order to address the contentious and difficult issue of the impact of information about medical use on non-medical use patterns. From the sponsor's perspective, there is little to gain financially from placing ads in major media outlets for a treatment that only a small number of geographically disbursed practitioners will be able to deliver, at least in the context of the Phase IV study in the several year period after initial FDA approval. Ads in publications targeted to the approved patient population or their physicians, however, could result in additional interest in the treatment and could prove beneficial to public health. Targeted ads would not be likely to trigger much in the way of non-medical use, since the ads would be announcing the availability of legal treatment with all the attendant safeguards and sensitivity to the needs of patients, with the further likelihood of insurance coverage paying the costs. No ads would be necessary if it were possible for the therapists trained in the delivery of psychedelic psychotherapy to treat a sufficient number of patients from among preexisting patients or through referrals and word of mouth.

The sponsor should also voluntarily offer to solicit FDA and NIDA input on ads prior to their actual use, though retaining the freedom to accept or reject the input received. If the issue of advertisements were to become a big concern to FDA or NIDA, the sponsor can consider whether to refrain voluntarily from advertising for some interim period. Discretion should be the guiding principle for the sponsor in order to generate the least amount of regulatory concern.

Media reports on beneficial medical treatments will probably prove more of an issue to NIDA than targeted ads to patients and their physicians. As one example of possible media attention, the TV news show *48 Hours* has indicated its intention to build a feature story around research into the use of MDMA in the treatment of anxiety and distress in cancer patients, once such research is approved.¹⁵⁸⁰ It is difficult to determine whether or not the sponsor should respond to media requests for information about a psychedelic drug's approved medical use. Most non-medical users of psychedelics are not aware of their therapeutic potential. If this information is disseminated in the media, a more respectful and less casual attitude toward psychedelic drugs may result in some non-medical users, reducing harmful use patterns. In other non-medical users, use might increase due to lowered credence given to other reports of the dangers of these drugs. In view of the

¹⁵⁸⁰personal communications, Ira Sutow, *48 Hours* Producer, beginning 12/21/94 and continuing through the present.

difficulty of determining the impact of information on the medical use of psychedelics on non-medical use patterns, the most appropriate policy might be to respond to media requests for information but refrain from proactively soliciting media interest.

Summary of Specific Regulatory Requirements

A series of recommendations have been made in this chapter for special restrictions on the use of psychedelic psychotherapy. FDA's authority to impose these regulations is anticipated to stem from the provisions of Subpart H of the accelerated approval regulations that enable FDA to approve certain drugs with restrictions to assure safe use. FDA should also seek a voluntary agreement from the sponsor to comply with these restrictions, so that the regulations will still be implemented if FDA's authority under Subpart H is ever ruled invalid by the Court. Such voluntary agreements, once entered into, would be binding.

These restrictions should include the following:

1) Phase IV Treatment Study

a) Commencing immediately after NDA approval, a Phase IV study should be required in which several thousand patients with the approved clinical indication are treated by an expanded and newly trained group of treatment professionals, under the auspices of an FDA-cleared IND or some similar authorization.

2) Distribution limited to psychiatrists with special training

- a) Only board-certified psychiatrists with special additional certification will be allowed to prescribe a psychedelic drug;
- b) The special training and certification program should be open to psychiatrists, clinical psychologists, social workers or anyone else licensed by the appropriate state authorities to provide psychotherapy or counseling;
- c) The psychiatrist will retain primary responsibility for the treatment, but can authorize other certified treatment professionals to work under his or her auspices;
- d) If the facility requires a director, that director need not be a psychiatrist but does need to be certified to deliver the treatment;
- e) The training and certification process shall be the responsibility of the sponsor;
- f) The training should last at least two full weeks, each week separated by at least four weeks;
- g) Training should include at least two patient treatment sessions in which the trainee assists a teacher and at least two patient treatment sessions in which the trainee takes primary responsibility for patient treatment under the direct supervision of a teacher;
- h) There should be a graduated license, a basic license for treatment providers who have chosen not to volunteer for a self-experience and a basic plus license for

treatment providers who have decided to volunteer for a self-experience, with the approved drug. There should be no difference in rights and privileges between the basic and basic plus license; and

i) There should be continuing education requirements in order to keep the certification active.

3) Distribution limited to use in facilities that meet minimum standards

a) Treatments shall be limited to facilities that are certified by the sponsor as meeting minimum standards;

b) Treatment shall not be limited to hospital settings or dedicated facilities;

c) Treatments should take place in a private room with attached bathroom;

d) The entire treatment facility should be reasonably private and soundproof;

e) The facility should provide comfortable accommodations for the patient to remain overnight; and

f) Treatments can take place in the patient's home or hospice center only in instances where the patient is too ill to travel to a licensed treatment facility.

4) Staffing requirements

a) At no time should a patient be left alone during the active phase of the treatment;

b) A minimum of two treatment professionals should be present in the facility during the active phase of the treatment session, though they need not both be in the treatment room;

c) Only one of the treatment professionals needs to be trained and certified by the sponsor in the delivery of psychedelic psychotherapy, the other could be in the process of being trained, certified and licensed;

d) If two patients are being treated simultaneously, three treatment professionals need to be in the treatment facility; and

f) A member of the treatment staff needs to spend the night in the facility whenever a patient does so, with no special training or certification required of this staff person.

5) Recordkeeping

a) The sponsor or third party paid by the sponsor should keep a complete registry of all patients and all treatment sessions, with the registry open for inspection by authorized personnel from the FDA and DEA;

b) Appropriate protections to protect the privacy of the patients shall be employed;

c) The reports on each patient and each treatment session shall be submitted to the sponsor or third party by the primary therapist for each patient;

d) A basic informational form for each treatment session should be submitted to the sponsor or third party by each treatment provider within one week of the treatment;

e) The report shall include information sufficient to determine whether the treatment

was for the labeled indication or an off-label indication; and

f) Each patient's primary therapist should submit to the sponsor or third party a standardized three-month follow-up data sheet.

6) Patients

a) Treatment sessions with the long-acting psychedelics as well as with MDMA shall require an overnight stay in the treatment facility;

b) Each patient should be required to fill out a brief self-report form one week after treatment and shall send it to the sponsor;

c) Each patient shall be required to fill out a brief self-report form three months after treatment and shall send it to the sponsor; and

d) Patients shall be limited to two sessions in any month, eight sessions in a year.

7) Off-label uses

a) No restrictions shall be placed on off-label uses; and

b) Off-label uses shall be reported to the sponsor.

8) Distribution through the mail

a) All medicines should be shipped by registered mail from the sponsor to the psychiatrist who prescribed the treatment; and

b) If the psychiatrist or primary therapist working under the direction of the psychiatrist is late in submitting patient reports, no additional supplies of the drug should be shipped.

9) Advertising and Media

a) Advertisements, if any, during the Phase IV study should be targeted to patients or their physicians, with a voluntary restriction on ads in general media; and

b) Advertisements should be submitted for comment to FDA and NIDA prior to their use. Sponsor should remain free to use any ad regardless of feedback; and

c) Sponsor may respond to media requests but should not proactively seek to generate media coverage during the time of the Phase IV study, and perhaps beyond.

Conclusion

After several decades of regulatory roadblocks, it is currently possible both in the United States and in several other countries to obtain permission to conduct clinical trials investigating the therapeutic potential of various forms of psychedelic psychotherapy. Rigorous, methodologically sound protocols can be designed, conducted and funded. Therefore, it is possible that some form of psychedelic psychotherapy may eventually be proven safe and effective in two adequate and well controlled investigations. A regulatory framework can be designed for psychedelic psychotherapy that will substantially reduce

misuse, abuse, diversion and the negative impact of information about the medical use on non-medical use patterns. With sustained, diligent effort, the regulations proposed in this chapter can be effectively implemented in practice, reducing many of the potential harms/risks. Indeed, most of the recommendations have parallels in existing regulations for other drugs or treatments, with modifications proposed to address their shortcomings. As a result, FDA approval of the medical use of a psychedelic drug as an adjunct to psychotherapy can make a positive contribution to the health of the American public and may set a precedent for further scientific investigations into the remarkable healing potential of the human mind.