# Human Hallucinogenic Drug Research in the United States: A Present-day Case History and Review of the Process†

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**Abstract** — Legitimate human research with hallucinogenic drugs, although of great theoretical and practical interest, involves daunting regulatory hurdles that have discouraged investigators from attempting such work. Using the example of the author's own application for and receipt of federal permission to administer N,N-dimethyltryptamine (DMT) to humans, this article reviews the application process, obstacles and their solutions, and the local and federal issues involved. Further human research with hallucinogens is possible if a persistent and collaborative effort is made with the relevant institutions that oversee the performance of this type of research.

**Keywords** — dimethyltryptamine, hallucinogens, human research, public policy

When I first considered initiating a human research project with N,N-dimethyltryptamine (DMT), an endogenous hallucinogen that has also been a drug of abuse, I was reminded by many professional associates of the pitfalls involving research with drugs in Schedule I of the Controlled Substances Act of 1970 (CSA). One leading authority on hallucinogen structure-activity relationships remarked to me in half jest that the sole paper he saw coming out of this attempt would be one describing the impossibility of such work in the present climate of war against drug abuse. The psychedelic research community, especially those whose orientation focuses on the use of these drugs as catalysts of the psychotherapeutic and/or creative process, is uniformly pessimistic with regard to human studies ever proceeding with Schedule I compounds, such as LSD, mescaline, psilocybin or DMT.

The CSA placed all medications and drugs of abuse into five categories or schedules, depending on their "medical utility," "abuse potential," and "safety of use under medical supervision." Schedule I is the most restrictive category into which drugs with no known medical use, high abuse potential, and a lack of demonstrated safety under medical supervision are placed. The CSA also provided a mechanism for the movement of drugs into and out of various categories. For example, tetrahydrocannabinol (THC) was rescheduled in the 1980s from Schedule I to Schedule II, after evidence of its efficacy in treating nausea and vomiting following cancer chemotherapy was convincingly demonstrated. However, methaqualone's rescheduling from Schedule III to Schedule I occurred as a consequence of its widespread abuse.

The placement of hallucinogens into Schedule I was controversial because studies had clearly demonstrated their safety under medical supervision (Strassman 1984). Although their medical therapeutic utility in several pathological conditions had not been irrefutably demonstrated, their use in research elucidating brain-consciousness issues was very promising. Nevertheless, further study of their potential utility for a variety of conditions could not be conducted after the CSA was passed; consequently, investigators were required to return their supplies of these drugs.

The abuse potential of these drugs was clearly high; it was this characteristic that seems to have been the major factor in their placement in Schedule I. Fortunately, animal

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research continued unabated, providing the focal point for the recent explosion of information about the neurotransmitter, serotonin, and its receptor subtypes in the brain. These receptors play a role in sleep, aggression, mood, sexuality, and psychosis, as well as the mechanism of action of the hallucinogens. Schedule I drug research with animals is significantly easier, and high-purity hallucinogens are available to qualified investigators from the National Institute on Drug Abuse (NIDA). The primary hurdles in the case of animal research are those involving Drug Enforcement Agency (DEA) requirements for security of the storage and/or disposal facilities, and making certain that those who will be handling these drugs do not have a criminal record.

## THE RESEARCH PROPOSAL

For clinical studies with humans, one needs to begin with a research protocol in which the rationale for hallucinogenic drug administration is described in detail. The protocol requires a clear statement of why one is interested in giving hallucinogens to people and what one hopes to measure or observe. One must be careful not to put the cart before the horse in this type of work. Psychiatric research workers sometimes spend excessive effort in applying drugs or other treatments of unknown mechanism of action to psychiatric disorders of tremendous heterogeneity, even within single diagnostic categories. Furthermore, basic psychophysiological mechanisms are inferred from research in psychiatrically ill patients before a clear understanding of the normal physiology of the variable under investigation is known. It is important to systematically investigate in normal subjects how hormones, drugs or other factors work before explaining pathophysiological states and treating or studying psychiatric patients.

Similarly, before suggesting that psychedelic drugs can cure everything from neurosis to hangnails, one is better served by first applying current tools of psychopharmacologic research to shed light on the basic effects of these drugs, both psychological and biological. Subsequently, these drugs could be prudently applied to disorders whose etiology or symptomatology interface with the known effects of hallucinogens. This approach seems more likely to provide useful data than a more seat-of-the-pants approach.

In my case, I approached the task of beginning a new human psychedelic drug research study from two angles. The first was from the vantage point of schizophrenia. In the 1960s and 1970s, DMT had been considered a prime candidate for the so-called endogenous schizotoxin. One theory suggested that overproduction of DMT might be related to the psychotic process seen in schizophrenic disorders (Gillin et al. 1976). Failure to demonstrate differences in DMT levels in several body fluids between normals and schizophrenics prompted the discontinuation of studies either giving DMT or measuring DMT levels. However, newer data concerning the role of serotonin in both endogenous and drug-induced hallucinations has provided a new approach to understanding the etiology of hallucinogenesis (Fischman 1983). At the most basic level, one might suggest that drugs that could block the hallucinations of DMT might also be antihallucinogenic in patients with schizophrenia. Thus, understanding how DMT worked in normals had relevance to a major public health problem.

I also approached a clinical study of hallucinogens from the drug abuse perspective. Hallucinogens continue to be used and abused by people in the United States, particularly in college-age populations (18-25 years), at about the same rate now as 20 years ago (Pope et al. 1990). In spite of the tremendous advances in understanding hallucinogens' effects and pharmacology in lower animals, the necessary interface of human psychopharmacology and animal neuropharmacology requires human studies. The human biology of these compounds has relevance to more specific treatments for acute adverse effects (e.g., the bad trip), understanding the effects of chronic use, and evaluating the effects of newly synthesized designer compounds as they appear on the street.

An important element of both of these approaches involved the development of a new rating scale for the effects of DMT, one that has less pathology-oriented ratings than previous scales. The Addiction Research Center Inventory (Haertzen, Hill & Belleville 1963), more or less the benchmark for assessing subjective effects of drugs in humans, contains what is known as the LSD Scale, which is commonly known as the dysphoria scale. Certainly hallucinogens can produce unpleasant effects, but they can be distinguished from other drugs by more than that quality. It seemed important to describe in more neutral phenomenological terms what actually is observed in the psychedelic state, particularly for subjects who seek out these drugs.

Both of these research directions also required basic dose-response investigations. Is there a relationship between dose and the effect of DMT, subjectively and biologically? Building on older clinical literature, interviews with experienced DMT users, and newer animal data, one might anticipate which experiences and biological effects would be seen. Dose-response studies could then be initiated. The biological factors I decided to examine involved hormonal (neuroendocrine) effects of DMT as downstream markers of effects on central serotonergic neurotransmission. I also speculated that serotonin receptor activation would be reflected in effects on basic vegetative variables, such as core body temperature, blood pressure, heart rate, and pupillary diameter. Subjective effects would be mea-

sured by the newly designed rating scale. This basic human research could provide the foundation for more detailed experimental interventions. Follow-up studies might include differential effects of DMT in selected patient populations with presumed abnormalities of serotonergic neurotransmission (e.g., schizophrenia, affective disorders, posttraumatic stress disorder), selective blockade of subtypes of serotonin receptors to begin assessing receptor subtypes responsible for specific neuroendocrine and subjective effects, and experiments in which repeated doses of DMT are administered in an attempt to develop acute tolerance to the drug.

A research protocol needs to provide an adequate discussion of background information (i.e., what is and is not known about the area to be investigated), hypotheses (findings that one hopes will be derived from the study and how these data will answer specific questions), a plan of investigation (what one will do and why), a consideration of risks and benefits to the subjects involved and how the risks will be managed (with plans to deal with adverse reactions), sample size determination, data management, references/bibliography, and an informed-consent document. Sample size determination and data management are relatively simple issues, if one has read the literature, has some idea of the direction and size of expected changes, and can consult with a qualified biostatistician.

University research offices have copies of U.S. Public Health Service Form 396, which is used in federal grant applications. This form contains an outline covering all the aspects of a research protocol, with clear explanations of what each area should include. It is the model research proposal format used by most nonfederal agencies as well. Most institutional review boards (IRBs), local committees that review the relevant human-risk issues, like to have proposals written in a similar format (although generally in less scientific detail).

In order to decrease the risks involved in this project my protocol involved using only experienced hallucinogenic drug users. Administering a drug like DMT to naive subjects seemed to be a high-risk venture. Level of experience was determined by an informal interview focusing on extent of psychedelic drug use as well as negative and positive effects experienced by prospective subjects. Special attention was paid to assessing the presence of defenses characteristically known to be associated with negative reactions to hallucinogens, specifically denial and projection (Barr et al. 1972). Furthermore, experienced subjects are better able to report on subjective effects and to compare and contrast their past experiences with DMT and/or other psychedelics. Finally, from a purely legal point of view, litigation claiming long-term brain or personality damage or subsequent problems with drug abuse would be less sustainable in subjects with extensive past use of psychedelics.

## LOCAL ISSUES

### The Institutional Review Board

Once the research protocol has been written (and hopefully reviewed and critiqued by knowledgeable colleagues), it must be reviewed and approved by the local IRB. This is a requirement for any research involving human subjects. The function of IRBs is to assure the safety of participating human subjects and, depending on the particular IRB, the scientific merit of the study. The latter element almost always is given greater attention by the scientific review committee of the research site in which the study will actually take place. The IRB may also recommend changes in and approves the informed-consent document that accompanies the protocol. Once approval by the local IRB and performance site is obtained, the process of obtaining federal approval can begin.

Issues with the IRB can be complex if one does not work within a university/medical school setting. The U.S. Food and Drug Administration (FDA) has published guidelines for university- and nonuniversity-affiliated IRBs. This information is available through the FDA's Office of Health Affairs. Nonuniversity IRBs may be local or may not be if local ones do not have the requisite expertise and/or it is a multisite study and the relevant IRB is at a different site. One can even hire an IRB that may work with nonuniversity-affiliated investigators, but they may charge exorbitant fees. If one is interested in creating an IRB, the requisite composition of an IRB is clearly defined in FDA guidelines. However, this is not recommended because it would create an unnecessary bureaucratic nightmare, independent of the major goal of receiving IRB approval. It is preferable to use an IRB that already exists.

From the outset, I had to explain to the IRB that even if I received their approval, I could not initiate any studies until the FDA and the DEA review processes were completed and their approvals obtained. Local approval was the necessary first step before I could submit my request to the federal review process.

The IRB at the University of New Mexico was most interested in the nature of the informed-consent document. They requested two things that were somewhat difficult to address. The first issue was that of Schedule I drug use in humans. If a drug has no medical use and cannot be used safely under medical supervision (the criteria for placement into Schedule I), how could I justify human research with it? They requested that I add the phrase "this drug has no known medical use" to the informed-consent document. I responded by referring to the hundreds of articles on the human use of LSD and nearly a dozen on DMT before the drugs were scheduled, demonstrating that they could be used safely under medical supervision, and that in many ways the Schedule I placement was not a medical

but a legal definition. I asked to be able to state only that it "had no *current* medical use," which they agreed to. Ultimately, I was able to remove even that phrase by arguing that if FDA approval was obtained, "no current medical use" was no longer true, as I would have demonstrated its utility as a tool for medical research.

The IRB's second concern was that I describe in the informed-consent document what the subjects might experience on the drug. Clearly, one can choose from the most hellish to the most beatific descriptions of the psychedelic drug-induced state, with a strong biasing effect on the subjects. I opted for a balanced description of effects of the range of symptoms, with a slight emphasis on pleasurable and interesting effects. I justified this more sanguine view by summarizing the results of my interviews with over 20 essentially normal DMT users, all but one of whom described their DMT experiences in an extremely positive light. There also were no published reports of serious psychiatric sequelae (e.g., psychosis lasting more than 24 hours) in normals given the drug. I did suggest the possibility of serious emotional reactions to the experience induced by DMT, and that in the most extreme case, psychiatric hospitalization was available. However, I was able to assuage the IRB's concerns slightly by emphasizing that these were quite experienced hallucinogen users, many of whom had had bad trips that had been informative and developmentally useful in their ability to manage subsequent experiences with psychedelics.

### The Performance Site Scientific Review Committee

More or less parallel to the IRB process is that of scientific review by the committee that oversees studies in the research center. My project was to take place in the General Clinical Research Center (CRC) of the University of New Mexico Hospital, funded by the National Institutes of Health to provide beds and nursing as well as laboratory and statistical support for CRC-approved human research proposals. Projects are submitted to the CRC Advisory Committee and need to follow the same general guidelines as do submissions to the IRB, with a naturally greater emphasis on the scientific rationale for the proposed project. There was less difficulty in obtaining CRC approval than IRB approval, as the CRC assumed that the IRB would address the overriding issues of risk and informed consent. The CRC requested an additional literature review to support my requests for measurements of the hormones I was interested in evaluating. They also wanted urine drug screens taken on the morning of every study day. This was not to disqualify people from participating in the study, but to be able to assess the effects of a positive urine on the parameters under scrutiny. Would a less robust prolactin response, for example, be associated with a positive urine screen for marijuana? The Advisory Committee also wanted me to impress on subjects the importance of not taking any other drugs of abuse during the project to keep the data as clean as possible.

### Confidentiality

One of the thorniest issues of the project was that of anonymity and confidentiality. Admitting to the use of Schedule I compounds is admitting the commission of a federal offense and being liable for prosecution. All of the subjects in this project are professionals, with spouses, families, reputations, and careers. Therefore, strict anonymity and confidentiality were required. Several meetings were held with the Medical Records Department, Legal Counsel for the University Hospital, Admitting Office, and Head Nurse of the CRC to discuss how to assure strict confidentiality and anonymity. Furthermore, it is usually required that the signed informed-consent document be attached to the subject's medical records, a situation impossible in this case. The final solution was complex but appears to be working well. A subject coming in for an admission medical history, physical examination, and laboratory work (i.e., blood count and chemistries, electrocardiogram, thyroid functions, urinalysis) has a chart made up with his or her real name. This is needed if at any time in the future the subject happens to visit the emergency room or clinics, then baseline medical data will be available for comparison. However, subjects' charts are not associated with my DMT protocol number. As I have run several projects through the CRC over the years, my being their physician of record is not in itself particularly incriminating. (I just as easily could have had another physician sign these forms; if this were the only project I had ever performed at the CRC, having me sign their papers might be seen as their admitting to the use of illegal drugs). The subjects' screening psychiatric examination as well as every admission for the project occurs under a code name and hospital chart number. Ultimately, the Medical Records Department allowed me to be the only person with the code. The more people who have confidential information, the more likely it will be compromised. I was also the sole possessor of the signed informed-consent documents and had to state that clearly on every admitting form.

The informed-consent clauses regarding confidentiality went through some evolution as the process unfolded. I had previously run a study giving melatonin, a pineal hormone and an experimental nonscheduled drug, in a clinical research setting that required FDA approval. In that case, I had stated that the FDA and the manufacturer of melatonin could have access to participants' medical records. In my first informed-consent document for the DMT experiment, I originally indicated that the FDA, DEA (as also involved in the regulatory process), and the manufacturer of DMT (at that time undetermined) might, under extraordinary circumstances, have access to the medical records.

This met with universal alarm. The following was the final solution to the issue of informed consent: if the FDA or the manufacturer was interested in interviewing subjects and/or having access to their medical records for scientific purposes, they would need to go through me, who then would determine whether or not individuals were indeed willing to do this. Records theoretically could be subpoenaed, but that would be vigorously fought. And, as I am the only one with the key to the code, I would refuse to divulge the key if this should occur.

### State Pharmacy Board Schedule I Permission

The last local issue was getting my state of New Mexico Schedule I permit, which is necessary before the DEA will process a Schedule I request. This varies from state to state, and the state board of pharmacy and/or the local DEA office knows if a state permit is necessary before applying for DEA approval. This was relatively easy. I submitted the appropriate form, including an abbreviated version of the protocol and approval letters from the CRC and IRB. This permission was granted at the board's next meeting.

## FEDERAL ISSUES

One should never send anything important to any federal agency by regular mail; always send it by express mail or with a return receipt requested. Also, always take detailed notes whenever speaking with anyone at any federal agency. Get names and phone numbers because one rarely gets the needed person the first time; he or she is often at the end of a long chain of in-house transfers from extension to extension. Write down as much as possible from every conversation. Refer to these phone calls in your mail correspondence to let the relevant agency know you are taking notes and to ensure accurate communication.

One will need to deal with at least two federal agencies in the application process: the DEA and the FDA. At times, their responsibilities overlap in vague and poorly defined ways. By going through the application process in a methodical and persistent manner, defects in this two-tier system became clearer and gradually worked themselves out. My overall impression of the process is that the difficulties I encountered were not due to intentional malicious roadblocking but uncertainty regarding who had final authority in a particular matter and what were the proper channels through which my request should be funneled. This, combined with generic bureaucratic inefficiency, resulted in a 21-month process from the date of application to final approval to begin the study. Even so, with my initial expectations, I was pleased that the process even went that quickly.

### Funding: An Aid to Obtaining Federal Approval

I submitted a research grant proposal to a nonfederal granting agency, the Scottish Rite Foundation for Schizophrenia Research, at approximately the same time I began the FDA-DEA approval process, which was in the spring of 1989. I would encourage all potential investigators in this field to consider a similar course. First of all, one's scientific reasoning is sharpened by the grant review process, and if the FDA and/or DEA review turns out to be inordinately long, the feedback obtained from the granting agencies' review boards may anticipate objections likely to originate at the federal regulatory level. If such a grant is approved, this enhances the likelihood of FDA/DEA taking note of the scientific credibility of the proposed work. I received a one-year award from the Scottish Rite Foundation to recruit subjects, develop a way to measure DMT in blood (the DMT assay), interview subjects who had smoked DMT in the past in order to draft a DMT rating scale, and pursue FDA-DEA approval. A second year was approved pending FDA approval. An application for a NIDA grant was made in June 1989. This was approved and funding started in May 1990, essentially at the end of the first year of the Scottish Rite grant. The NIDA grant then took over where the Scottish Rite grant left off, a fortunate case of good timing. Both these awards were extremely helpful in prompting the FDA and the DEA to pay more attention to my request to get started with the experiments.

### The Drug Enforcement Administration: The Schedule I Permit

DEA approval, although slow, was not particularly complicated. There is an application form specifically for Schedule I drugs (DEA Form 225: Application for Registration Under Controlled Substances Act of 1970) that is available from Washington or the local DEA branch. This is different from the routine Schedules II-V form that all medical practitioners use to obtain approval to routinely prescribe controlled substances (e.g., opioids, benzodiazepines). There is a four-digit code number for all scheduled drugs that needs to be placed in its respective box on the form. Not everyone at the DEA knows these numbers. I did not realize it at the time but the back of the front page of form DEA 225 has a list of many scheduled compounds (including DMT) with their respective drug codes. Should there be any difficulty in determining the correct drug code number, one can call the Registration Branch of the DEA in Washington. I was inadvertently given the National Drug Code number for DMT by the DEA in Washington over the telephone. My entire application packet was returned to me a month after I submitted it with a request for the right number, accompanied by a piece of paper with all the appropriate numbers for my information. Along with this properly completed form an abbreviated version

of the protocol needs to be included, along with IRB and scientific review committee letters of approval. One also needs to describe the security arrangements for storing and handling a Schedule I compound, which the pharmacy can provide on their official stationery.

After several months of phone calls, inquiring as to the status of my application, I learned it had been sent to the regional DEA office in Denver. From there, it was sent to the local DEA office in Albuquerque. The local DEA agent assigned to my case then came out to the University of New Mexico a couple of times. She inspected the security system in the pharmacy (and found some weaknesses in the system that required correction), instructed that a special freezer with its own lock be purchased that was to be placed in the controlled-substances vault in the pharmacy (which was already kept locked and guarded 24 hours a day), interviewed me and the manager of the pharmacy, and requested the names, addresses, social security numbers, and phone numbers of all the people who would have access to the DMT and/or have keys to the freezer (several laboratory personnel and pharmacists, primarily; I do not have a key to the freezer). She then ran security checks on me and all those whose names were provided to check for any criminal records. After being satisfied with the security checks, locked freezer, and improvements in the security system, she described to me the consequences of poor record keeping and unexpected losses of drug supplies. She wrote an approval letter to the DEA office in Washington. After a month or two of keeping track of this letter, I encountered another unexpected difficulty.

My project required laboratory-grade DMT for the assay, which I could purchase from Sigma Chemical without difficulty once I received my Schedule I order forms. This form of DMT did not need to meet the many requirements necessary for human administration. It could be taken off the shelf of a chemical supply house and used directly for laboratory or animal work. The project also required getting permission to obtain and possess clinical-grade DMT for human administration. This form of DMT needs to be certified by the FDA as safe for human use. However, the DEA had no recent experience processing a request for administering a Schedule I drug to humans and had difficulty in differentiating the two requests. They were reluctant to let me order laboratory-grade DMT until I had received FDA permission to go ahead with the human study. However, FDA approval for this could not occur until I found a source for, and established the safety of, a clinical-grade DMT. I asked the FDA for their help in interfacing with the DEA's pharmacist, and finally succeeded in getting the DEA to distinguish between the two requests. Soon thereafter, I was issued my Schedule I permit, with order blanks, and could order DMT from Sigma Chemical for the laboratory. Once I received FDA approval to begin human administration of DMT (from, at that point, an unknown source) I was to notify the DEA of this but no additional paperwork was required.

### The Food and Drug Administration: The Investigational New Drug Application and the Drug Master File

The application process with the FDA involved two steps. Usually, if a drug is used for a purely experimental study, an Investigational New Drug (IND) application needs to be submitted. This was quite simple in the case of my previous melatonin study in 1985. At that time, I worked with Sigma F & D, a division of Sigma Chemical, who had a Drug Master File (DMF) for melatonin on file at the FDA. After I spoke with and wrote to Sigma they authorized the FDA to access their DMF on melatonin on my behalf. The FDA looked at the manufacturing data, chemical purity tests, and other information on melatonin in the DMF and then gave me permission to order the melatonin. After the pharmacy prepared it in a solution appropriate for injection, I tested the sterility and pyrogenicity (ability to cause fever), sent in this information, and shortly thereafter received permission to proceed with the study.

Since 1985, and particularly since the early 1970s, when a group at the National Institute of Mental Health (NIMH) received permission to give DMT to humans, regulations have become much stricter at the FDA, particularly regarding injectable drugs. DMF requirements are more elaborate and require a full pedigree of the compound (i.e., statements regarding the source and purity of all precursors, assessment of purity and identification of contaminants in all intermediary synthetic compounds, and more documentation regarding the composition and characteristics of the final product that would ultimately be given to subjects). Therefore, when I submitted my IND application for DMT, I again believed that Sigma F & D would be able to provide the drug and that the process would be analogously simple. I spoke with and wrote to Sigma F & D, who agreed to set up a DMF for their DMT. I sent in my IND application forms, along with copies of the IRB and scientific committee approvals, a copy of the informed-consent document and a brief description of the study, hoping that the FDA would accept Sigma F & D's information.

The forms used to apply for an IND are FDA 1571 and 1572, each of which is two pages long. Form 1571 contains an interesting clause that might be of use when trying to study drugs that have been previously investigated. This clause, which can be checked as part of an application procedure, is a "request for reinstatement of an IND that is withdrawn, inactivated, terminated or discontinued." DMT had been studied by a group of investigators at NIMH in the 1970s (Gillin et al. 1976) and another

group in Chicago had used the NIMH IND for a series of their own studies somewhat later (Meltzer et al. 1980). I thought that I might be able to use information from the old IND to speed the approval process for my own application.

Documents sent to the FDA enter via the Documents Room, and from there letters are routed to the appropriate division. In the four years since my melatonin IND was issued, a new division has been formed for Pilot Drug Evaluation, to which my DMT IND application was referred a week or two after its arrival in Washington. The FDA then sent me a standard form letter acknowledging receipt of the application, the name of the drug for which the application was made, and the IND number. It was signed by the responsible Consumer Safety Officer (CSO) with a phone number and routing address. (Never fail to write the IND number on the top of any future correspondence with the FDA. Without it, letters will languish forever in the Documents Room awaiting someone who has the time to figure out what the IND number is and, by default, where it needs to go.) This letter stated that unless I heard from the FDA within 30 days of the date stamped on the top of the form letter (generally 10-15 days after sending the application) I could proceed with the study. This is standard procedure for the FDA on receipt of any IND application.

At this point, it is necessary to begin intensive telephone contact with the review section staff. I began calling as soon as I received the name of my project manager (PM). Of course, the main problem with the IND application was that I had no source of drug, and the FDA could not grant me permission to begin a study without the DMT. It was therefore on "Hold" (an official FDA term) from the outset. However, I needed to begin finding out who could make the drug, and what information I would need to send to the FDA concerning the compound. Within a couple of months, I received a detailed letter from the FDA requesting the necessary information regarding preparation of the bulk drug, and the characteristics of the clinical form of the drug that I actually planned to administer.

The two primary contacts one first works with on the section staff are the CSO (or PM) and the chemist. The FDA has two charges in a case like this: the first is to assure the safety of human subjects, and the second is to give some scientific guidance to optimize the chances that the experiments with humans will provide valid and valuable data. A chemist is involved because no drug company makes Schedule I drugs for human use anymore. My request was linked to the finding of a source for the actual drug; the chemist needed to help me with this process. Even if a drug company was making the drug, the FDA chemist would still be involved in assessing and examining the DMF to assure that the drug was safe for human use. Safety in this context means assuring that the drug is in a high state of purity (99+%) and contains no toxic impurities. The chemist must evaluate the manufacturing process and analytical data (the chemical pedigree) for the drug in order to certify these requirements. The PM, on the other hand, interfaces with the scientific staff at the FDA regarding scientific matters.

I was aided in the area of scientific concern by virtue of having received IRB and CRC input and approval. I also was fortunate to have received the Scottish Rite and then NIDA funding for the project. The review processes involved in these grants sharpened the science of the project, and funding from outside agencies greatly enhanced my credibility.

## The Search for Clinical-Grade Dimethyltryptamine

Acquiring the DMT for the study was a complex process, and at one point in time I began to fear that the whole project would come to a dead end because satisfactory DMT could not be obtained. When a drug has been made for human use, be it by a pharmaceutical company or a private concern, the FDA has a DMF on it, containing detailed information regarding synthesis of the drug and its pedigree. Drug companies have large chemistry laboratories that provide this information to the FDA, and they are familiar with the process of setting up a DMF for any particular compound. The DMF also contains information regarding animal and human toxicity data, when relevant. Fortunately, in the past, DMT had been given in numerous animal studies and nearly a dozen human studies. Therefore, the toxicity issue did not concern this particular drug.

My IND application was complicated by the fact that it was necessary to establish a DMF for the DMT, in addition to acquiring permission to give the drug for an experimental purpose. If a study was designed to use a drug currently in use (e.g., morphine) for research on a nonindicated use (e.g., to control high blood pressure in an emergency setting), a drug company could simply authorize the FDA to access their DMF on the researcher's behalf. However, no DMF existed for DMT. One hope I held out was that I might acquire DMT from some source, and if it were not pure enough, I could purify it to the required level. However, at a very early stage in the negotiations it was clear that this was not satisfactory to the FDA. The pedigree and detailed synthetic information had to be provided.

With the aid of the FDA chemist, I was able to track down (in the Federal Archives Building) the old IND for DMT that was used at NIMH in the 1970s. Recall that I was hoping to reactivate an expired IND, using data acquired by NIMH researchers. However, the information in that IND was wholly inadequate for current FDA requirements: there was no DMF in their IND. The IND file said that Aldrich Chemical in Chicago had made the DMT

for the NIMH study. I contacted Aldrich, but they had never compiled a DMF for the drug nor did they distribute the compound anymore. The NIMH group, whom I subsequently contacted, no longer had either their IND records or any information regarding the drug.

Sigma F & D, as described previously, was willing to supply the FDA with as much information as it had available regarding their DMT in order to set up a DMF on the compound. However, they did not actually manufacture the drug; a source in Europe supplied it to them. The European source was unwilling to provide detailed information regarding their synthesis of the drug. Therefore, Sigma F & D was ruled out as a source of DMT that could set up a valid DMF.

NIDA has made scheduled drugs available for animal studies, and has in fact supplied investigators with a non-hallucinogenic LSD analogue for human positron-emission tomography studies (Wong et al. 1987). However, NIDA's DMT that was on the shelf was relatively old and did not have the pedigree and required synthetic information that the FDA required.

However, NIDA has a contract with the Research Triangle Institute (RTI) in Research Triangle Park, North Carolina. RTI provided the THC for the marijuana/THC protocols in the 1970s that investigated the effects of these drugs on nausea and vomiting induced by cancer chemotherapy. However, when I contacted RTI on NIDA's referral, they initially claimed they could not make drugs for human use because of liability concerns, but I was told by NIDA that not one suit has ever been brought against NIDA for the marijuana/THC study. Although NIDA expressed their general concern about the lack of any reliable source of high-quality drugs of abuse for human studies, they stated that research with DMT was not of sufficient priority for them to pay RTI to make the drug to the specifications required by the FDA, even if RTI did agree to make it. Therefore, I would have to pay for the preparation. These discussions with RTI and NIDA took place before my grant from NIDA was approved and funded. After some negotiating, RTI agreed to prepare high-quality DMT and send me the information necessary to set up my own DMF for the drug. They estimated the cost of such a synthesis, including the record keeping, to be "in the thousands," which was quite out of the range of my ability to pay. Thus, RTI and NIDA were also effectively ruled out as sources for clinical-grade DMT.

Next, I tried NIMH, which has a Chemical Synthesis Program to make obscure research drugs for investigators. Again, their contract stipulated that their drugs, even if prepared to the most exacting specifications, could not be used in humans. However, the director of this program stated that he was considering changing the wording of their contract when it was up for renewal to be able to provide drugs for human studies. This might be a source of such drugs for future investigators and should be pursued, but NIMH also had to be ruled out as a source of DMT for my own study.

I then asked a colleague with experience in synthesis of hallucinogens within a university setting if he would consider making the DMT for my project. He declined, referring to the difficulties involved in acquiring a manufacturer's license through the DEA to distribute scheduled drugs. I approached another colleague with similar experience within a university setting. He had been keeping abreast of my futile search and was aware that I had about exhausted all possible avenues. He finally agreed to consider making DMT to FDA specifications at cost, and thereby considerably less than the RTI quote. However, manufacturer's licensing procedures are much stricter than regulations concerning individual laboratories' research use and he wanted assurance that making the drug for me would not break any DEA regulations. After some effort, I found a division within the DEA, the Office of Drug Research Registration, that regulates registration issues for researchers. They informed me of the "coincidental activities" clause within their regulations that allows registered researchers to prepare small batches of scheduled substances for collaborative research efforts rather than the sale-for-profit context of a manufacturer-purchaser relationship.

At this point, when asked whether or not this would be a satisfactory arrangement from the FDA's point of view, the FDA chemist referred me to a physician on the drug abuse staff in the FDA's Pilot Drug Division. He believed such an arrangement would be satisfactory. He also quickly became my most important, responsive, and reliable liaison within the FDA.

My colleague who agreed to manufacture the DMT and I then submitted brief amendments to each of our DEA applications that would justify the preparation and possession of adequate amounts of DMT for a collaborative research effort. We needed to provide the DEA with the reason for requesting this amendment, the amount of DMT involved, and a statement to the effect that this was a research, not a fiduciary, relationship. A tremendous number of phone calls was required to keep this amendment moving through the maze of sections at the DEA. One major delay was the DEA's request that the FDA approve this amendment. The FDA did not believe this was necessary, although the DEA would not proceed past a certain point until they received, in writing, FDA approval of this amendment. I do not know where the truth actually lies in this case, although the FDA complied with the DEA's request.

DEA approval was thus obtained for my colleague to produce DMT. Several months later, I received eight grams of DMT-fumarate (a form of DMT that FDA has approved for human use) and all the supporting documentation of

the synthesis and analysis of this material necessary to set up a DMF in support of my IND. The University of New Mexico Hospital Inpatient Pharmacy then prepared a dosage form of the DMT suitable for injection into humans. This was a sterile nonirritating solution that was distributed into 50 sterile vials.

Finding out how many samples to subject to quality control was difficult. Guidelines at the FDA generally refer to pharmaceutical companies' massive lots of a drug. After some discussion with the Pilot Drug Division and several other divisions within the FDA, it was agreed that I would use two vials each for the four tests necessary on the clinical form of the drug. The following were the four tests: (1) Content Uniformity — Is the measured concentration in the vials actually that calculated? (2) Purity — Is the drug pure and/or free of potentially toxic chemical contaminants? (3) Sterility — Are there bacteria, yeast or other pathogens in the solution of DMT? (4) Pyrogenicity — Are there fever-producing bacterial fragments in the solution? A fifth and related test is that of Stability — Are purity and content uniformity maintained over time? The rigorousness of these criteria was in part determined by the fact that the drug was going to be injected, not given orally. If the drug were to be given orally, some of these requirements would have been relaxed.

Purity and content uniformity can be performed on the same vials. The University of New Mexico Hospital Toxicology Laboratory agreed to perform these tests using equipment already available for measuring levels of abused drugs in clinical samples (e.g., blood, urine). Most toxicology laboratories have the requisite gas chromatography, mass spectrometry or high-performance liquid chromatography equipment necessary for such work. Any clinical microbiology laboratory can perform the necessary sterility testing for aerobic and anaerobic bacteria, yeasts/fungi, and actinomyces (similar to tuberculosis). The fact that DMT is a Schedule I drug and the results were to be used to determine safety for human administration dissuaded the University of New Mexico Hospital Microbiology Laboratory from conducting these tests. However, the New Mexico State Laboratory's Environmental Microbiology Section agreed to provide this service. Pyrogenicity is usually determined by injecting a rabbit with a predetermined amount of drug and then measuring its temperature. However, DMT raises body temperature in rabbits (as do all hallucinogens) by a pharmacological mechanism, independent of pyrogen presence. Another test, the limulus amebocyte lysate (LAL) test, can be performed in a test tube and is also FDA approved. Two laboratories with LAL expertise refused to handle a Schedule I drug; a third agreed (Scientific Associates of St. Louis). It is important to make certain that a quantitative result and raw data for the LAL test are obtained. A simple presence or absence result is not adequate.

Stability testing can occur concurrently with the study and samples will be submitted for purity and concentration checks one and two months after preparation of the drug solution, and at three-month intervals as long as the study is proceeding. The pharmacy, as well, needed to prepare a report describing their preparation of the clinical form of the DMT. Finally, my colleague had to prepare a large file on the drug's preparation, its pedigree, the qualifications of those who made it, and several tests as to its purity and identity.

I organized all of these reports, wrote a cover letter to the FDA addressing each issue brought up in their letter notifying me that the IND was on hold, and mailed it. As the study was on hold, the FDA was required to respond within 30 days of receiving my letter. A letter with the accompanying data is called, in these cases, an amendment to the IND. I received written approval to proceed within two weeks of submitting this amendment. I began the study accordingly.

At the time of this writing, the study is nearly half completed. This particular phase of my work with DMT will end in early 1992. Hopefully, the remaining DMT can be used in future studies of its effects in humans. These future studies will require CRC, IRB, and FDA approvals. Because there is an existing supply of DMT, which I am able to administer safely, I do not anticipate major problems in beginning other studies.

## CONCLUSIONS AND FUTURE DIRECTIONS

A question that comes to mind while reviewing this process is, What if the drug *has* been made by a pharmaceutical company (e.g., LSD by Sandoz)? Does Sandoz have the information to set up a DMF? Would they test whatever remaining available drug exists for the FDA? Would the expiration date on their lots of LSD have passed, thus voiding their use? I do not know, but using a drug company's compound would certainly bypass the difficulties I encountered in finding an approved manufacturer of the drug, not to mention all the chemistry, toxicology, bacteriology, pyrogen testing, and clinical formulation work.

What can one learn from this, at times, Kafkaesque process? First, with perseverance, it is possible to acquire permission to conduct human research with a hallucinogen; in this case, DMT. Second, personal contact, primarily by phone and carefully followed-up mailings are the best ways to help the process keep moving forward. Such contact is required, especially to convince the FDA, DEA, and at times NIDA, to speak with one another on the researcher's behalf. Third, a simple, scientifically well-reasoned approach with in-house approval is essential, and outside funding is very important. Fourth, a close collab-

orative relationship with someone who can manufacture hallucinogens may be necessary. Drug companies, if they do make the drug, might be inclined; however, it is better to have a first-class medicinal chemist with a university affiliation. Again, outside funding and the possibility that the project might dead-end without my colleague's assistance were very important factors in persuading him to take on this daunting task.

For researchers interested in studying the use of hallucinogens to enhance the psychotherapeutic or creative process, I believe that using the same approach, tedious and plodding as it is, might be similarly applied. There have been well-validated advances in psychotherapy and cognitive science research in the past 20 years. Standardized treatment protocols and testing procedures are effective in teasing apart salient issues in psychopathological states. Carefully blending the relationship between the effects of hallucinogens on cognitive, emotional, and interpersonal variables with the processes involved in standardized psychotherapy techniques (or creative problem solving) could be combined in attempting to use these compounds for such purposes.

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