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REVIEW

Regulation of human research with LSD in the United States (1949-1987)

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Abstract Human research with hallucinogens such as lysergic acid diethylamide (LSD) has been ongoing in the USA since 1949. During the 1960s, LSD was investigated for a variety of psychiatric indications, including the following: as an aid in treatment of schizophrenia; as a means of creating a "model psychosis"; as a direct antidepressant; and as an adjunct to psychotherapy. Studies with all drugs, including LSD, have always been conducted under federal regulatory controls, including the 1938 Food Drug and Cosmetic Act (FDCA; which ensured the safety of drugs) and the 1962 Kefauver-Harris Amendments to the FDCA (which described appropriate scientific methodology and ensured drug efficacy). This paper details how the 1962 Amendments introduced numerous safety and efficacy requirements that must be in satisfied during clinical drug research—and how human studies conducted with LSD in the 1960s struggled with their fulfillment. Information is provided from Senate hearings, case law, and interviews with key investigators. Examples are also drawn from scientific papers and symposia published during and since that period, with a focus on information from clinical studies conducted with LSD by psychiatrist Albert Kurland at the Spring Grove State Hospital, near Baltimore, MD. While Kurland largely conformed with these new regulations, other investigators often fell short of complying with scientific standards and federal requirements. Thus, the human hallucinogen studies of the 1960s are best understood as providing pilot data on safety and efficacy, as well as testable hypotheses for current hallucinogen studies conducted under modern scientific and regulatory standards.

Keywords Hallucinogen · LSD · Clinical · Regulation

Every month, it seems there is another story in the news heralding a clinical study being conducted in the USA with a hallucinogenic drug. Some of these studies are engaged in evaluating the potential medical applications of hallucinogens, while others are investigating scientific questions that are pharmacological or psychological in nature. But all of these studies have one thing in common: as modern clinical studies, they are being conducted under an investigational new drug (IND) application, an oversight mechanism by the Food and Drug Administration (FDA) for human research with drugs. These hallucinogen studies additionally all have approval by an Institutional Review Board (IRB) to ensure subject safety, all study participants have signed an informed consent document, and the research is being conducted under a Schedule I license from the Drug Enforcement Administration (DEA), among other regulations. This was not always the case, though.

This paper will discuss how changes in FDA policies in the 1960s that oversee all drug research in the USA introduced numerous safety and efficacy requirements that affected clinical research with hallucinogens such as lysergic acid diethylamide (LSD). (LSD is the focus of this paper because there is vastly more historical information available compared to psilocybin or mescaline.) This review uniquely and systematically evaluates these studies in terms of their compliance with the new regulations. These regulations critically improved scientific standards and subject protections, which led to the curtailment of many unethical research practices common at that time for clinical research with any class of drugs. This is an important history

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because FDA has often set the standards for human research and drug development for the rest of the world. However, for reasons detailed below, laboratories that wished to continue conducting human studies with LSD in this era often struggled with the fulfillment of specific elements in the new regulations. This ultimately led to a decline in LSD research.

Although we may wish to excuse the methodological discrepancies in the older hallucinogen studies as being from another era, we cannot do so and at the same time treat the data from these studies as valid and reliable for informing modern regulatory decision-making. Thus, the early studies with LSD are best understood as providing valuable pilot data on safety and efficacy, as well as testable hypotheses for future studies conducted under current scientific and regulatory standards.

The early years of LSD treatment and research

The history of research with hallucinogens in the USA is exemplified by how LSD was investigated in humans in the years following its famous rediscovery (and colorful bicycle ride) in 1943 by its inventor, Swiss chemist Albert Hofmann at Sandoz Pharmaceuticals (Hofmann, 1983). It was only a few years later, in 1947, that the first scientific study was published on the effects of LSD in 16 healthy volunteers (to observe their responses) and in 6 patients with psychosis (to see if it would alter their symptoms) (Stoll 1947). The principal investigator, Swiss psychiatrist Werner Stoll, also tested the drug on himself, so that he might experience a schizophrenic state of mind. Two years later, in 1949, Boston psychiatrist Max Rinkel and Los Angeles psychiatrist Nick Bercel personally brought the first Sandoz LSD to the USA for testing (Lee and Shlain 1985; Hagenbach and Werthmuller 2011).

Under the 1938 Food Drug and Cosmetic Act (FDCA), before a drug could be marketed nationally in the USA, drug companies needed to submit data to FDA under a new drug application (NDA) demonstrating the safety of their drug. (For regulatory purposes, a "new drug" is one that has not been approved in the USA, regardless of how old the drug actually is or whether it has been approved in other countries. It also includes FDA-approved drugs that are proposed for a new indication, formulation, dose, or patient population.)

Notably, the FDCA provided for an exemption to the restriction on distribution. Drug companies were allowed to distribute drug samples nationally, prior to NDA approval, if they were "intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety of drugs" (FDCA, Sec. 505 (i), 21 U.S.C. § 355(d)). In fact, this manner of interstate distribution—a company sending drug samples to a doctor, who then tried them on a patient—is how thalidomide came to be tested in pregnant women in the USA. This resulted in children with phocomelia, despite the fact that an NDA was never approved for thalidomide because of the heroic actions of FDA medical reviewer Frances Kelsey in 1960 (Kelsey 2014).

Many companies utilized this system of distributing investigational drugs, including Sandoz. This meant that even though Sandoz never submitted an NDA, samples of LSD were shipped (under the trade name Delysid) to psychiatrists in the USA starting in 1949 for their experimental use on patients.

At the beginning of USA sample distribution, LSD had a very limited research history, so psychiatrists often tested the experimental drug in any patient group that intrigued them. In doing so, psychiatrists were acting as though LSD was a marketed drug with demonstrated safety that they were just using off-label for untested indications in patients they wished to help. The breadth of psychiatric hypotheses to which the unique properties of LSD were applied at that time included the following: as an aid in the treatment of schizophrenia; as a means of creating a "model psychosis"; as a direct antidepressant; and as an adjunct to psychotherapy.

Experimental applications of LSD

Relation of LSD to psychosis

In order to appreciate why LSD was investigated in relation to schizophrenia, it is instructive to read the drug label written by Sandoz that accompanied investigational samples of LSD (Hofmann 1983):

Indications and dosage

(a) *Analytical psychotherapy*, to elicit release of repressed material and provide mental relaxation, particularly in anxiety states and obsessional neuroses. The initial dose is 25 μg (1/4 of an ampoule or 1 tablet). This dose is increased at each treatment by 25 μg until the optimum dose (usually between 50 and 200 μg) is found. The individual treatments are best given at intervals of 1 week.

(b) *Experimental studies on the nature of psychoses*: By taking Delysid himself, the psychiatrist is able to gain an insight into the world of ideas and sensations of mental patients. Delysid can also be used to induce model psychoses of short duration in normal subjects, thus facilitating studies on the pathogenesis of mental disease. In normal subjects, doses of 25 to 75 μg re generally sufficient to produce a hallucinatory psychosis (on an average 1 μg/kg body weight). In certain forms of psychosis and in chronic alcoholism, higher doses are necessary (2 to 4 μg/kg body weight).

Both of these indications were studied with great enthusiasm by psychiatrists with little else available to treat psychosis or to understand the condition. Given that over 1000 papers had been published on the effects of LSD in humans by 1963, it is not simple to determine how well the study designs and treatment of subjects comported with current standards of protecting patient safety. However, focusing on evidence from key clinical researchers with LSD provides insight into what was deemed to be acceptable at that time.

Aid in treatment of schizophrenia

The first paper published in English with LSD was in 1950, reporting on a human study conducted by St. Louis psychiatrists Anthony Busch and Warren Johnson (Busch and Johnson 1950). They recounted that they had been looking for a drug that could exogenously induce a "transitory delirious state," after observing that patients who were experiencing an endogenous "toxic delirium" could participate more easily in psychoanalysis. During this search, the authors report that, "Sandoz Company called to our attention and made available d-lysergic acid diethylamide." The report describes the responses of 29 patients, most of whom were diagnosed with schizophrenia. The dose of LSD ranged from 300 μg (women) to 400 μg (men). These doses are far beyond those recommended by Sandoz. (For context, the typical recreational dose of LSD ranges from 50 to 250 μg). In the published paper, no safety procedures are given. No information is provided regarding the preparation of subjects, the method of selecting doses, or the means of evaluating changes following LSD exposure. Using their clinical judgment, the authors conclude that LSD "re-activates anxiety and fear with apparently just enough euphoria to permit recall of the provoking experiences."

Although LSD was given with therapeutic intent to patients with psychosis through the 1960s, there is little evidence that it produced beneficial results. As Canadian psychiatrist and LSD researcher Abram Hoffer observed in 1970, "LSD ought to make people with schizophrenia much worse. It does, in fact, do so." (Hoffer 1970).

"Model psychosis"

The ability of hallucinogens to produce a "model psychosis" was first observed in 1927 by the German psychiatrist Kurt Beringer, who coined the term in relation to the experimental effects of the hallucinogen, mescaline (Beringer 1927). One of the first papers in English on this topic reported in 1952 that LSD produced "psychotic phenomena" in healthy individuals (Rinkel et al. 1952). The prospect that LSD was "psychotomimetic" (could produce psychotic-like responses) was of great interest to scientists. As noted by the psychiatrist and LSD researcher Daniel Freedman in 1970, "One of the great inducements of such research was the hope that if one could chemically induce a grossly altered behavioral state, then clues might be gathered about where to look in nature for the biochemical factors of clinical disease (such as schizophrenia) which resemble, but are not identical to, the LSD state" (Freedman 1970).

However, as Nobel-prize winning biochemist Julius Axelrod observed, "The first problem I worked on was the metabolism of LSD, [which] at that time in psychiatry was very fashionable. They thought this would give you the clue to schizophrenia, but a very astute psychiatric nurse can tell the difference between anybody who took LSD and amphetamine, because LSD doesn't resemble schizophrenia at all—but amphetamine does" (Axelrod 2003).

By 1956, Canadian psychiatrist and LSD researcher Humphrey Osmond concluded that LSD needed to be reframed away from its association with the induction of madness. He then created the new term "psychedelic" (meaning "mind-manifesting"), to replace "hallucinogen," which he felt conveyed that LSD produced a hallucinatory state of psychosis (Novak 2004). (This paper uses the term "hallucinogen" because it is the regulatory classification used in the Controlled Substances Act of 1970; CSA)

Antidepressant and adjunct to psychotherapy

LSD was proposed as a direct daily pharmacotherapy for depression by Swiss psychiatrist Gion Condrau in 1949. This form of LSD treatment was proposed without counseling, based on the ability of the drug to produce mood elevation through euphoria (Hagenbach and Werthmuller 2011). This LSD regimen did not produce the desired antidepressant results, however. Even Hofmann concluded that "LSD does not act as a true medicament; rather it plays the role of a medicinal aid in the context of psychoanalytic and psychotherapeutic treatment" (Hagenbach and Werthmuller 2011).

In the period spanning the 1930s to 1960s, numerous drugs were proposed as "adjuncts to psychotherapy," including stimulants (Pohlman 1957), barbiturates (Lehmann 1993), and benzodiazepines (Tone 2009). Thus, it is not surprising that LSD was similarly proposed as an adjunct to psychotherapy, based on its unusual psychological effects, as shown in an exchange between psychiatrists and LSD researchers Albert Kurland and Sol Kramer in 1967 (Kurland and Unger 1967):

> *Kurland*: We definitely do not see LSD being utilized here as a medication in the usual sense. Rather, it is conceived of as an activating mechanism that brings about a unique experience ... upon which the therapeutic intent and structuring is focused...
> *Kramer*: The way I interpret this [is] that it is the psychedelic experience, and not the LSD pharmacology per se, which produces the antidepressant effect.

There were two sequential approaches to psychotherapy with LSD: "psycholytic" and "psychedelic." As described

by Faillace (1966), psycholytic therapy administered 50–200 μg of LSD to patients once or twice a week prior to therapy, for a duration up to several months, with all sessions conducted in a special area of a hospital. Although the effects of LSD can last up to 12–16 h, psycholytic sessions lasted only 4–8 h because they were attenuated with either a barbiturate or an antipsychotic such as chlorpromazine. In contrast, psychedelic therapy was conducted differently, with patients undergoing daily psychotherapy for weeks prior to a single administration of 400 μg of LSD in the same special hospital setting. During a psychedelic session, the ability of LSD to "abolish the distinctions between... self and world" was thought to produce "an overwhelming transcendental experience." The session continued for the full duration of the effects of LSD, guided by a "specially trained" therapist who was able to guide "the intensive reaction... in a very short period of time." The LSD session was often followed by more psychotherapy to integrate the experience.

These two therapeutic approaches are consistent with both "second force" (psychoanalytic) psychology and "third force" (humanistic) psychology perspectives, which emphasize "the unconscious" and/or "self-actualization" and identity (Goble 1970). These perspectives stand in contrast to "first force" psychology (behaviorism), which focuses on observable behavior, not thoughts and feelings. While scientific research from a behaviorist perspective is centered on quantifiable data, psychoanalytic and humanistic perspectives on research consider psychological meaning and purpose to be paramount. The contrast between these orientations to research (the primacy of data vs. the production of meaningful experiences) underlies the difficulties that LSD investigators underwent as regulations were strengthened.

Regulations to protect subject safety and scientific integrity

The regulation of human drug research, as elaborated by FDA and the International Conference on Harmonisation (ICH) under "good clinical practice," has two primary goals (FDA/ICH 2015). The first goal is to assure that the rights, safety, and well-being of study subjects are protected, consistent with the ethical principles of the Declaration of Helsinki. The second goal is to confirm that the study design is scientifically appropriate, in order to produce scientifically valid data. In the absence of adequate study methodology, the risk in exposing the subject to an unapproved drug cannot ethically be justified.

Since the beginning of the 1900s, the medical establishment in the USA had been discussing how best to protect the safety of individuals who participate in scientific research. One advance was a 1935 Supreme Court case that made a legal distinction between scientific investigations and medical malpractice, as long as the study design did not "vary too radically" from "accepted methods"—and that the patient provided consent (Fortner v. Koch 1935). Although the 1938 FDCA established that FDA needed to determine that a drug was safe before it could be marketed, it did not require animal toxicity testing prior to human experimentation and it did not specifically address the safety of subjects who participated in research.

Beginning in 1958, Congress began to hold hearings that eventually focused on the quality of drug company-sponsored clinical studies (especially because companies justified high drug prices on the basis of the high cost of research). These concerns culminated in the 1962 Kefauver-Harris Amendments to the FDCA (which took effect in February 1963).

The primary advance of the 1962 Amendments was establishing that FDA needed to determine that a drug was not only safe before marketing, but that it was also effective for a specific medical indication. Prior to this, the "efficacy" of a drug was determined by the clinical judgment of a physician treating an individual patient. The AMA stood against the 1962 law, stating that "the only possible final determination as to the efficacy and ultimate use of a drug is the extensive clinical use of that drug by large numbers of the medical profession over a long period of time" (Green and Podolsky 2012).

Robert Temple, the current Deputy Center Director for Clinical Science at FDA, has stated that the agency could have interpreted the 1938 FDCA safety regulations as support for the need for efficacy, based on a risk/benefit analysis (Temple 2011). But in practicality, the need for a company to demonstrate drug efficacy was only applied selectively prior to 1963. In addition to efficacy, the 1962 Amendments established that all premarketing drug studies with humans (whether in patients or "normal controls") needed to be conducted under an IND.

Notably, the 1938 FDCA prohibits the distribution of drugs that are adulterated or "misbranded" (have a label that is false or misleading) into interstate commerce. This means that an NDA is not only a compilation of all nonclinical and clinical scientific data to support the marketing of a drug—it is also an application to allow for interstate transport of the drug. The 1938 FDCA provides a mechanism so that unapproved drugs (such as drug samples) can be transported across state lines for research purposes without violating the law. This is called a "Notice of Claimed Investigational Exemption for a New Drug," which is actually the legal name for an IND (Junod 2008).

To stop toxic drugs (like thalidomide) from being distributed anymore as samples, the 1962 Amendments allowed interstate delivery of investigational drugs only if the nonclinical safety testing data submitted to FDA was adequate to justify the initiation of drug use in humans. Under an IND, investigators also had to agree not to share the drug with other investigators (Junod 2008).

The IND process is separated into Phase 1 studies (with healthy volunteers to evaluate safety) and Phase 2 and 3

studies (with patients to evaluate safety and efficacy). At the end of research, all nonclinical and clinical study data and study protocols are compiled to create the NDA. An NDA is submitted to FDA when a sponsor believes it can demonstrate the safety and efficacy of a drug for a particular indication at specific doses.

Given that LSD has never been a marketed pharmaceutical with an FDA-approved NDA, this paper will focus on the methodology of clinical studies conducted under an IND with LSD before and after the 1962 Amendments.

These new regulations were needed because, as FDA's Frances Kelsey reported, "many clinical trials were poorly performed [prior to 1962] .... I was quite shocked at the caliber of the work that had gone into the applications in support of safety" (Kelsey 2014). While the IND requirements were extensive (see below), they were vague about how a researcher might fulfill each aspect in practicality.

This meant that FDA reviewers were left to interpret what specific kind and amount of information drug companies or investigators needed to provide in order for a clinical study to proceed under an IND. Coming out of the 1950s, high-level FDA officials were typically former inspectors who did not have medical or scientific degrees (Hilts 2003). At the reviewer level, FDA did employ some physicians, but "they kept up their private practice and [were at] their FDA desks only part-time" (Hilts 2003). (FDA subsequently hired qualified scientists and physicians.) Prior to the 1962 law, there was often a much-too-friendly tone taken between drug companies and FDA. As Frances Kelsey recalled, "It was very common for reviewers... to go out to lunch at fancy restaurants with the drug firm representatives. There was an end to that by the time I came [in 1960], but I still used to hear tales of eating at the Rive Gauche" (Kelsey 2014).

The requirements of an IND, as described in Part 312 of the Code of Federal Regulations (CFR; 21 CFR 312), include information regarding: the drug's chemistry and manufacturing, animal toxicology, the proposed clinical study protocol, and the qualifications of the investigator and research facility. Additionally, investigators had to commit to personally conduct or supervise the study procedures, and provide timely submission of adverse event (AE) reports. Other requirements were added in 1963 for signed informed consent from subjects and in 1966 for independent subject safety oversight by an IRB.

After the IND requirements had taken effect in 1963, many investigators who had been administering LSD to patients did not feel it was necessary to "prove" to FDA that LSD was reasonably safe in order for them to continue running human studies. As the FDA reported following a 1964 visit to psychiatrist and LSD researcher Harold Abramson, "He feels that he, as a doctor, may administer any drug to his patients in the course of treatment and that the government hasn't any jurisdiction in the matter." (Schorr 1964). By this time, there were hundreds of clinical studies published in the medical literature reporting that LSD did not produce serious overt physiological distress in most humans. Nonetheless, investigator belief did not satisfy the modern regulatory standard that determined whether a drug can be deemed "safe" for use in clinical trials.

Similarly, "efficacy" of an experimental drug is not determined by clinical judgment, but instead is based on FDA evaluation of data from "adequate and well-controlled investigations" (21 CFR 314.126) conducted under an IND. This includes the following: evaluation of subjects with a specific medical condition; use of a standardized test drug and control condition; adequate sample size, treatment duration, and treatment design (parallel or crossover); randomization of subjects to treatment conditions; blinding; submission of a full protocol; and appropriate statistical analysis of data. These criteria were affirmed as appropriate by FDA in 1970 (35 Fed. Reg. 7250).

Despite what appears to be a specific list of requirements for an appropriate clinical study, Hilts (2003) reports that "it took more than two decades before the letter of the 1962 law was being observed," such that the "art of clinical trials" was invented as investigators and regulators went along. A decade after the 1962 Amendments, the Supreme Court weighed in on these issues, similarly concluding that "clinical impressions of practicing physicians and poorly controlled experiments do not constitute an adequate basis for establishing efficacy... Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered as corroborative support of well-controlled studies" (Weinberger v. Hynson 1973).

What follows below is a detailing of the various elements that are necessary to satisfy the requirements of an IND regarding appropriately conducted clinical studies—and how investigators who wished to conduct human studies with LSD in the 1960s struggled with their fulfillment.

IND: chemistry and standardization of study drug

Gaining access to a standardized experimental compound, with known chemistry and synthesis, is often the key step in determining whether a human study can be considered. In the 1960s, access to LSD changed dramatically from what it had been in the 1950s. This produced a very complicated history, as described below.

Sandoz submits INDs for LSD

As noted by FDA Commission James Goddard at a 1966 Senate Committee hearing on LSD, Sandoz first made FDA aware of LSD in 1953, following their distribution of the drug to European psychiatrists. The purpose of the FDA visit by Sandoz was "to discuss clinical investigations Sandoz was planning to pursue in the United States... The Sandoz representatives told us that the great power of this drug contained in

very small doses led them to believe it should be available only to qualified research psychiatrists. Our agency agreed completely."

Following the passage of the 1962 Amendments, Sandoz submitted an IND for LSD in 1963 (Carpenter 2011). As required, the IND would have included information about the drug's chemistry and manufacturing with regard to the standardized ampules and tablets that Sandoz had been distributing as samples to clinical investigators. This information, however, was proprietary and therefore not publicly available. Thus, researchers who wished to continue using LSD in human studies did not have access to the necessary chemical information required for submission of their own IND. This meant that researchers would need to obtain a letter of authorization (LOA) from Sandoz in order to establish a "right of reference" to the chemistry data.

Sandoz, however, was not interested in giving LOAs for their proprietary and patented LSD chemistry to most researchers who wanted to conduct human studies with LSD. In 1962, Sandoz had established a committee of trusted investigators to advise on whether researchers who wanted to test LSD were "competent to work with the drug" based on scientific "standards of practices" (Buckman 1966). If a researcher did not pass Sandoz's muster, they would not receive a LOA, and therefore could not get an IND and gain legal access to Sandoz LSD. This left many researchers who had conducted LSD studies in humans angry and frustrated, especially after the way Sandoz had freely distributed the drug previously.

Although precursor chemicals to synthesize LSD were widely available in 1963 (Hagenbach and Werthmuller 2011), use of LSD from any source other than Sandoz would have been illegitimate for research purposes at that time because they were the only entity who had submitted chemistry information under an IND. Without FDA approval of the drug source (and drug label used for distribution), any LSD purchased from sources other than Sandoz would have been "misbranded," a violation of the FDCA.

Illicit sources of LSD for research

Many clinical laboratories ceased LSD research when they could not obtain the drug legally. Some researchers still had large supplies of Sandoz LSD, but refrained from using it without an IND in their own name. This was because, as they were cautioned by Rudolph Bircher of Sandoz in a 1965 symposium, "Your malpractice insurance, if something should go wrong, would never cover it." (Murphy 1967). (It is notable that Bircher did not appear troubled by use of his company's experimental drug with patients prior to 1963).

Some investigators who were especially invested in maintaining their human LSD research sought access to LSD through illicit sources. Shortly before the Amendments took effect in 1963, Myron Stolaroff of the International Foundation for Advanced Study (IFAS) in Menlo Park, CA, concluded that they might not be able to submit a successful IND and continue their investigations because of the lack of a LOA from Sandoz. This meant they would not be able to legitimately obtain Sandoz LSD. The LOA may not have been forthcoming because of investigator qualifications. As required for all drug studies, IFAS did have a physician on staff: psychiatrist Charles Savage, who would go on to do LSD research at the National Institute of Mental Health (NIMH) and Spring Grove State Hospital, near Baltimore, MD (see below). But some of the other IFAS investigators who were heavily involved in running the LSD sessions (as if they were psychotherapists) had no actual mental health credentials. FDA informed IFAS that, "In our opinion, the proposed co-investigators... Alfred M Hubbard and Myron Stolaroff, do not possess necessary qualifications for undertaking the proposed clinical investigations" (Harvey 1965). This was because Stolaroff was an engineer (formerly with the electronics company Ampex) (Walsh and Grob 2005), while Hubbard was an engineer who had purchased a "medical degree" from a fake university (Lee and Shlain 1985).

Stolaroff decided to make contact with Bernard Roseman and Bernard Copley, who promised to sell him LSD made by underground chemists (Roseman v. United States 1966). When the two men arrived in Menlo Park after a trip to Canada, they sold two bottles of LSD to Stolaroff for $600 each, as well as a sample of LSD to an undercover federal agent. The men were arrested, based on violations of the FDCA (among other laws). Notably, they were not charged for selling a controlled substance because such laws did not yet apply to LSD.

In the trial that followed, the men claimed they could not be prosecuted under the FDCA for misbranding because FDA had no jurisdiction over LSD that had been synthesized and sold within the borders of California (in other words, without interstate commerce). The government disagreed (saying the drug had been obtained either from Israel as the men had originally asserted, or from their trip to Canada) and the men were sentenced to 17 years in jail.

Interestingly, no charges were placed against Stolaroff for seeking to obtain an experimental drug from an illicit source. It is likely this occurred because Stolaroff appears to have turned state's witness. According to Tim Scully, a well-known underground LSD chemist, "Roseman believed Al Hubbard had convinced Myron Stolaroff to turn [him and Copley] in to the FDA" (Scully 2013). Unbeknownst to Scully, the truth of his allegations had actually already been confirmed in 1966 when FDA Commissioner Goddard testified about the Menlo Park case during Senate hearings on LSD. Goddard stated, "Two men offered to sell... [LSD] to a [psychotherapist]. This man reported the incident to us. One of our agents contacted the sellers. They came to his house all set to make a big sale. They were promptly arrested." (Goddard 1966).

As psychiatrist and LSD researcher Abramson stated at a conference in 1965, "It's virtually prohibited now for a private physician to use LSD unless his patient buys it on the black market ... I have had patients who tell me, 'If you won't give me LSD, I'll get it and then come in.' Naturally, I disapprove of this" (Murphy 1967).

Further restriction on access to LSD

In 1965, Congress passed the Drug Abuse Control Amendments (DACA) to the 1938 FDCA, which allowed FDA to regulate depressants, stimulants, and hallucinogens. In 1966, the LSD precursor chemicals lysergic acid and lysergic acid amide also came under control through this law (US Bars Distribution 1966). DACA was passed following the creation of the Bureau of Drug Abuse Control, an enforcement arm within FDA that was a precursor to the DEA. This law prohibited the manufacturing, compounding, processing, or sale of the cited drug classes unless permitted by the government for wholesale distribution, research, or medical applications (through an IND, for example). This meant that doing human research with LSD without an active IND would be in violation of DACA. Although DACA was a precursor to the 1970 CSA (see below) and the 1971 international treaty, Convention on Psychotropic Substances, it did not penalize personal use or possession of the listed drug classes.

Sandoz withdraws their IND

By August 1965, Sandoz decided to stop production and distribution of LSD. This was in part because their patent had expired in 1963, but also was in consideration of "the flood of requests" for the drug (Hofmann 1983) and the rising incidence of LSD use for recreational purposes. In their public statement, they said: "Despite the outstanding properties of [LSD], or rather because of the very nature of these qualities ... the usual means of practical exploitation could not be envisaged. In spite of all our precautions, cases of LSD abuse have occurred ... completely beyond the control of Sandoz, [reaching] the scale of a serious threat to public health" (Hofmann 1983).

In April 1966, Sandoz notified FDA that they wished to withdraw their IND for LSD. This action was a formalization of discussions that had already occurred with federal officials, who had orchestrated a means through which investigators approved by Sandoz would be allowed to continue LSD research in humans. Under this program, according to Stanley Yolles, Director of NIMH, the remainder of the Sandoz LSD supplies in the USA were delivered to NIMH by armored car in April 1966 (Yolles 1966). The 21 g of LSD that NIMH then possessed was estimated to have a street value of $300,000 ($2.3 million in 2017 dollars). This amount of LSD was enough to supply 210,000 doses of 100 μg each to acceptable laboratories conducting human research.

In newspaper coverage of these events, it was reported that, "Sandoz... regrets that it has to withdraw the investigational drug applications for LSD and will no longer be able to supply even qualified medical investigators" (Schumach 1966). Despite this assertion, Sandoz subsequently provided LOAs to 17 investigators they deemed acceptable, who were then able to submit their own INDs and successfully receive LSD for their clinical experiments (Goddard 1966). According to FDA Commissioner James Goddard at the 1966 Senate hearings on LSD, Sandoz had decided that their policy for providing an LOA and for providing LSD would be based on an investigator having grants or authority from NIMH, the Veteran's Administration, or state agencies to conduct LSD research in humans, as long as it occurred in a carefully controlled environment, such as a hospital (Goddard 1966).

Goddard testified, "There were about 70 projects approved prior to Sandoz withdrawing from direct support and investigation of the drug. There are now, I believe, 9, with 12 investigators." This statement reflects that out of the 17 investigators who had been given LOAs by Sandoz, a total of 9 INDs for clinical studies with LSD were submitted and allowed to proceed by FDA. This meant that these investigators could keep their current supplies of LSD and apply for additional drug as necessary in order to complete their studies. Sandoz supplied the LSD in ampules that contained a 100 μg/ml solution of LSD, as well as in tablets that contained 25 μg of LSD (Hollister 1968). However, as Frances Kelsey testified at the 1966 Senate hearings, if a Sandoz LOA was not obtained, "all the investigators listed in that IND were required to stop their studies and turn back their LSD" (Kelsey 1966). Eventually, Sandoz extended their right of reference to grantees of "other approved national agencies" such as the National Science Foundation, expanding the number of INDs submitted by qualified investigators to 53. It is not possible to determine from public records whether these INDs were primarily submitted from investigators who had previously worked with LSD or were instead from new investigators. However, all proposals for new clinical studies with LSD underwent "dual review" by both NIMH and FDA (Goddard 1966).

FDA-PHS psychotomimetic advisory committee

In 1967, NIMH separated from the National Institutes of Health (NIH) to become its own bureau in the Public Health Service (PHS), with status equivalent to that of NIH (NIH Almanac, 2016). That same year, the FDA-PHS Psychotomimetic Agents Advisory Committee (PAAC) was formally established with representatives from FDA, NIMH, and up to 12 nongovernmental mental health and pharmacology professionals (US Makes LSD More Available 1968). The PAAC met six times a year and determined whether proposed

animal and human studies with hallucinogens and cannabis were scientifically valid and whether investigators would be allowed to access study drugs from NIMH supplies.[1]

The PAAC was put in place in 1967 specifically to expedite the processing of study applications compared to the old system. According to psychiatrist Kurland at Spring Grove State Hospital, "It isn't too difficult to do research in this area if you submit a protocol… If [the studies] meet the judgment of your scientific peers, they will be approved. Whether it will be funded is another matter" (Debold and Leaf 1967).

IND: scientifically designed clinical studies

In the USA, the federal government was heavily involved in funding clinical scientific studies with LSD. According to the 1966 Senate hearings on LSD, Kurland was provided with large multi-year grant funding from NIMH for his LSD studies with alcoholics ($142,056 from 1964 to 1967) and with neurotics ($309,472 from 1965 to 1968). In general, NIMH-funded clinical studies with LSD in the 1960s tested a limited number of subjects, used patients with loosely diagnosed psychiatric disorders (or they accepted patients with a wide variety of disorders), and often did not use a valid control condition (which prevented both the randomization of subjects into groups based on a parallel or crossover design, as well as the ability to conduct a statistical analysis).

Thus, none of the NIMH-funded clinical studies with LSD from any laboratory qualified as "adequate and well-controlled" for evaluating safety and efficacy at the level expected for studies submitted in an NDA. Therefore, these human studies are best characterized as either hypothesis-generating individual case reports or as small pilot studies. Even Sandoz never conducted systematic Phase 1 safety studies or sufficiently large Phase 2 and 3 efficacy studies to determine whether specific doses of LSD administered to a patient population with a particular medical condition produced statistically significant changes compared to placebo on standardized outcome measures.

This means that it is difficult to discern the strength of the safety signals or evaluate evidence of efficacy from these early published clinical studies with LSD. In part, this is because the standards for scientific reporting on clinical studies were often much less rigorous than they are today and relied heavily on the judgment of the clinical investigators (rather than on validated outcome measures). Additionally, as mentioned above, the standards for all drug research at that time were poorly defined or enforced. Thus, these scientific issues were not isolated to clinical research with hallucinogens or psychiatric conditions in general.

Given the limitations of evaluating human LSD study procedures as published in the medical literature in the 1960s, it would be ideal to be able to directly analyze the original clinical protocols as submitted in an IND. Unfortunately, out of all the INDs for human studies with hallucinogens that were submitted to FDA in the decade immediately following the 1962 Amendments, only a few are still readily available for scrutiny internally by FDA personnel. Additionally, all information submitted under an IND is held as confidential and FDA cannot even disclose the existence of an IND unless it had been publicly acknowledged (21 CFR 312.130). Although individuals can request information under the Freedom of Information Act (FOIA), FDA can only make a disclosure determination regarding which information from an IND is releasable when it processes the FOIA request. There are additional challenges to FDA's disclosure evaluation when the principle investigator is dead or an institution has dissolved.

Based on these limitations, it is not possible to publicly present specific information from a clinical study with LSD that is only available through an IND submitted to FDA. This is unfortunate, since the information contained in the INDs for LSD that are available internally at FDA creates a riveting narrative about the investigators and regulators as they negotiate on the clinical studies. However, it is possible to deduce from publicly available information whether an investigator had an IND. For example, as described above, it is known from the 1966 Senate record that Kurland received extensive NIMH funding in the mid-to-late 1960s for his LSD studies in alcoholics and neurotics. This means that he was eligible to obtain a LOA from Sandoz in order to receive LSD. He subsequently published numerous clinical studies with LSD in the scientific literature. Since he could not have legally conducted these investigations after 1963 in the absence of an IND, it is clear that FDA must have allowed his studies to proceed under an IND, based on submission of an LOA from Sandoz. Thus, it is instructive to evaluate his publications in terms of how well his studies conform with the 1938 and 1962 FDA regulations in light of current scientific standards.

Animal toxicology testing

Currently FDA does not allow clinical studies to begin until a test drug has undergone sufficient animal toxicity testing to predict that the drug can be safely administered to humans. However, in the years immediately after the 1962 Amendments, the degree of nonclinical toxicology necessary before clinical studies under an IND were allowed to proceed was variable.

[1] This system will be familiar to any current cannabis researcher whose non-NIH funded study protocol was required to go before a modern version of the PHS committee in order to obtain botanical marijuana from the National Institute on Drug Abuse (NIDA). (NIDA was originally founded in 1973 within NIMH, after it had rejoined NIH). This modern iteration of the PHS committee had representatives from NIDA and FDA, but was abolished in 2015 in a federal effort to streamline marijuana research.

Starting in the 1950s, Sandoz had extensively distributed samples of LSD, despite the lack of extensive nonclinical data demonstrating that the drug was not toxic. During FDA evaluation of the Sandoz IND for LSD in 1963, the agency initially considered terminating the IND, since the company had submitted very limited animal toxicology data (D'Aguanno 1963). However, agency reviewers argued that there was already extensive clinical experience with the drug. Given that these studies suggested the possibility of efficacy without serious AEs or deaths, the Sandoz IND was supported by FDA. In retrospect, it is interesting that the Sandoz IND had a paucity of nonclinical toxicity data for LSD, given that FDA only allowed other investigator-led clinical studies with LSD to proceed if they had right of reference (through an LOA) to the animal data in the Sandoz IND—or they had generated their own animal toxicity data.

At FDA, Kelsey was hesitant on the clinical use of LSD because of the dearth of data from animal reproductive toxicology studies. She was no doubt sensitized by her experience with thalidomide, especially when allegations emerged of chromosome damage resulting from LSD use. In March 1968, Kelsey was quoted in the Wilmington Morning News (Delaware) that "no definite causal relationship has been established [between LSD and chromosomal changes]", but that FDA was testing pregnant monkeys with LSD (FDA Aide Links LSD 1968).

As described by psychologist and LSD researcher William Richards (2015), an evaluation of reproductive toxicity from LSD was conducted in 1969 by his research team in Kurland's laboratory at Spring Grove State Hospital. They used a double-blind, FDA-approved study protocol (in collaboration with NIH) that tested blood from 32 subjects before and after LSD psychotherapy (Tjio et al. 1969a). Their study showed "there is no definite evidence that pure LSD damages chromosomes of human lymphocytes in vivo". It is likely that this study, as well as similar studies and reviews (Tijo et al. 1969b; Long 1972; Dishotsky et al. 1971) were instructive in the decision of FDA to allow LSD research to continue. To date, there are no credible data supporting the allegation that LSD alters genetic material.

A controlled study of LSD therapy with alcoholics

Kurland's group published two papers based on their study evaluating LSD as an adjunct to psychotherapy with a large number of alcoholics: a preliminary report in 1967 with 69 patients (Kurland et al. 1967) and a final report in 1971 with 135 patients (Kurland et al. 1971).

According to the published papers, the alcoholic patients first received intensive psychotherapy "nearly every day" for 2 weeks, for a total of 12–20 h with a "specially trained" therapist. Once "the quality of the therapeutic relationship [had] opened," the LSD session was scheduled. The protocol specifies that the study uses a "psychedelic procedure," in which the patient would receive LSD at either 450 μg (the test drug condition) or 50 μg (as the active control condition) in a double-blind design. In a latter phase of the study, some patients were allowed to receive up to two additional LSD sessions if they participated in 6 months of outpatient therapy.

During an LSD session, the patient was extensively monitored by the therapist and a nurse for 10–12 h, while listening to music in a "comfortable living room" setting at the hospital while wearing eyeshades or interacting with the therapist. Patients received "a heavy dose of tender loving care," which the researchers believed was "a highly significant ingredient in the mobilization of psychedelic reactions." The study evaluated changes in the patients before and after LSD sessions using 12 psychological tests that measured personality, "intelligence functioning and impairment".

LSD produced improvements in those individuals who received either the treatment dose (450 μg) or the active control dose (50 μg). Undefined evaluations of "drinking behavior" showed improvement in 121 of 135 patients who were available for follow-up in both LSD groups, but the degree of change, as well as baseline drinking to qualify subjects as alcoholic, were not provided. This was reported as being statistically greater in the high dose group at 6 months. But by 12 and 18 months after treatment, there were statistically similar high degrees of improvement in average "drinking behavior" for individuals in both LSD groups. With regard to safety, the paper reports that "only one adverse reaction" was reported by any of the 135 patients who received LSD, but that AE and its management are not described. This strongly suggests that clinical judgment, rather than use of a list of AEs that occur commonly or rarely in clinical studies, determined if a mentionable AE had occurred.

Choice of control condition and blinding

The Kurland alcoholic study raises the issue of the value of an active control compared to (and especially in lieu of) a placebo control. One purpose of a control condition, in combination with blinding, is to reduce possible bias by both subjects and investigators regarding the impact of treatment. Yet as observed by psychologist Richard Yensen (who later joined Kurland's group as an investigator), "Double-blind controlled studies have been demonstrated to be an inappropriate methodology for studying LSD, because it is not feasible to create an effective blind for LSD with either an active or inactive placebo" (Yensen and Dryer 1992).

Although controlling bias is important, a more important scientific purpose of a control group is to determine whether changes in outcome measures during a study can be attributed to the experimental treatment, or rather to other factors (FDA 2001). This is why most modern psychiatric drug studies only evaluate behavioral or psychological changes produced by the

test drug in comparison to a neutral placebo—even when the test drug produces AEs (such as anticholinergic effects or sedation) that easily distinguish active from inactive treatment. Placebo controls have been the gold standard in clinical studies since the 1950s (Shorter 2011).

In Kurland's study with alcoholics, both doses of LSD (the threshold dose and the psychedelic dose), in conjunction with psychotherapy, reduced "drinking behavior" 12–18 months after drug treatment. However, by not including a placebo condition, it is not possible to determine whether LSD is efficacious in reducing drinking no matter what dose was given (even barely noticeable ones), or whether LSD had no effect at all and the long-term positive responses are attributable to the intensive therapy. Thus, it cannot be determined whether LSD was better than no drug treatment, even though the blinding of the investigators and subjects was managed.

Informed consent

As early as the 1950s, researchers recognized that adequately informing a potential subject about an LSD study would be difficult, given the individualized responses produced by the drug. There were two schools of thought at that time on the question of whether, or how, to obtain consent for study participation. On the one hand, many patients who received LSD in that era were told that they were receiving a novel treatment, but not that they were participating in research. The identification of the drug as LSD might not be conveyed to patients—or it could be the *only* information conveyed, without details of its effects (Abramson 1967).

For example, when LSD was tested in schizophrenic patients for ostensibly therapeutic purposes, the patients were unlikely to be informed that the drug might exacerbate their psychotic symptoms. In psychologist Betty Eisner's memoire of her work with hallucinogens (Eisner 2002), she recounts how a patient was "on the verge of a psychotic episode." Despite concerns that LSD treatment could "blow him into a paranoid schizophrenic psychosis," the team physician decided that since the patient was "heading in that direction anyway," "there's nothing lost if we try." Similarly, when LSD was being given to opioid-addicted prisoners at the Addiction Research Center in Lexington, KY, to evaluate its psychoactive effects, the subjects were not usually informed about what they were receiving or what to expect. This likely accounts for the reason why the "LSD" scale on the Addiction Research Center Inventory (ARCI) of subjective responses to drugs represents "dysphoria" responses.

On the other hand, for those who believed LSD might have a valuable role in psychotherapy, providing some knowledge about the drug effects was part of the proper preparation of a subject so that the LSD session would be beneficial. This is known as the "set and setting" for an LSD session, referring to the mindset of patients and the environment in which they would experience the drug. As observed by Yensen and Dryer (1992), the degree of enthusiasm of the investigator was often recognized to influence the therapeutic outcome from LSD treatment.

After the 1962 Amendments took effect in 1963, investigators were required to obtain written informed consent from subjects prior to their participation in a study. However, the concept of consent with LSD is complicated when the investigator cannot predict how any particular person will respond to the drug. Investigators might also produce an "undue suggestive effect" that can adversely affect the therapy (Barrigar 1964).

According to Kurland's published papers, the study patient was given an "informational and expectation-structuring" packet of articles about LSD treatment. He was informed of the study procedures and the effects of LSD, including possible "alarming reactions" and other general AEs. (The patient was always a man because FDA policy in the years immediately after 1963 did not allow women of childbearing age to participate in drug studies, based on fears of teratogenicity in the wake of the thalidomide crisis (FDA 2017)). Kurland acknowledged that in the early days, informed consent "wasn't as elaborate as [it was] later" (Kurland 1997). This would be consistent with many consent documents of this era that do not contain genuine safety information for the potential subject to consider—or inform the patient that the test drug was investigational. Instead, the text often appears to be primarily in service of releasing the research unit of legal responsibility for AEs (Campbell and Stark 2015).

Use of LSD by investigators

In 1966, FDA Commissioner Goddard testified at the Senate hearing on LSD that, "Reports of nonmedical use of LSD [by investigators] had come to FDA as early as 1961." This practice was surely enhanced by the Sandoz drug label for LSD, which explicitly encouraged investigators to test the drug on themselves so they would be familiar with its effects.

In 1969, Kurland's group initiated a program in which mental health professionals would be allowed to receive one to three LSD sessions in order to better understand unconscious processes and improve their own therapeutic skills and empathy (Yensen and Dryer 1992). In an oral history, Kurland recalled that some on the Spring Grove staff wanted to be exposed to LSD so that it might "enhance [their] capacity for interacting" with patients (Kurland 1997). Kurland told them this would be run scientifically, saying, "Before anybody gets involved, we're going to have some rules. The rules are, you have to go through a procedure just like the patient. You have to be interviewed by a number of psychiatrists." All told, according to Yensen and Dryer (1992), "203 professionals received one to three LSD sessions in this program between 1969 and 1976" at Spring Grove. Many of these individuals reported "considerable benefits from their LSD sessions".

Self-experimentation outside of regulated studies was also common at this time. Prior to joining Spring Grove, psychologist Sanford Unger was at NIMH and took LSD while there, along with his section chief and the director of clinical investigation (Neill 1987). Unger later said, "It seems necessary, unfortunately, in 1968, to say at the time, 1962, it seemed not only logical or desirable, but even a respectable course of action" to try LSD (Unger 1969).

Conclusions

For over 70 years, scientists have been fascinated with the unique pharmacological and psychological effects of LSD and other hallucinogens, as well as their potential therapeutic applications. Currently, when INDs are submitted to FDA for human studies with hallucinogens, they are evaluated according to a variety of regulations dating back to the turn of the last century. These regulations are the same ones that govern all drug research and are applied in a neutral fashion, even for a drug class like hallucinogens that carries cultural baggage. The bottom line for FDA in determining whether a study may proceed is based on whether the studies are designed and conducted in a manner that protects subject safety and will produce valid scientific data that justifies the risk to the subject.

There is no doubt that complying with myriad rules and regulations can be time-consuming and frustrating for an investigator who wishes to conduct a clinical drug study. But the reason these regulations were developed over time was not to delay the ability to initiate research. Regulations were established to prevent the exploitation of human beings for intellectual curiosity, unethical financial gain, or worse. Since the 1960s, many other regulations have been put in place, including ones ensuring study subject "rights and welfare" through IRB oversight, as well as restrictions on research with children, prisoners, and other vulnerable populations. These regulations are in place to assure that human rights are upheld during clinical research and that the experiments will produce scientifically valid data.

Although the 1962 Amendments to the 1938 FDCA listed specific methodology required for human drug studies, these were not immediately adopted by most clinical sites in the way we understand them now, regardless of the type of drug being investigated. When the published clinical studies with LSD in alcoholics from Albert Kurland's group at Spring Grove State Hospital are examined, it is clear they are among the best of that era in that they attempted to conform to the regulations for "adequate and well-controlled" studies. However, by modern standards, his published study reports do not provide information on the amount of alcohol consumption used to qualify subjects, or on randomization, informed consent, IRB approval, monitoring and management of AEs, justification of outcome measures, amount of drinking after treatment, and statistical evaluation of data.

Although we may wish to presume that all research groups that were allowed by FDA to conduct hallucinogen research were as scientifically dedicated as Kurland's, much of the hallucinogen research in this period falls short of ideal scientific methodology. This is not a modern observation, however. There were many published reports in the years following the 1962 Amendments that criticized the general scientific integrity of the ongoing LSD studies, including from hallucinogen investigators at NIMH and Spring Grove:

- Jonathan Cole (NIMH): "We must stress that none of these claims [for LSD] are based on detailed, carefully controlled studies. None of [the hallucinogens] have been proved to be effective or safe therapies for any psychiatric condition." (Cole and Katz 1964)
- Sanford Unger (NIMH and Spring Grove): "Not a single, methodologically-acceptable controlled study of the efficacy of LSD-assisted psychotherapy has yet been performed. The many claims of dramatic therapeutic changes... must thus be regarded as not proven." (Unger 1964)
- Charles Savage (Spring Grove): "Nearly all studies [with hallucinogens] have serious shortcomings... [which] include: 1. anecdotal evidence; 2. inadequate assessment procedures; 3. insufficient follow-up; 4. naive statistical treatment; 5. lack of controls." (Savage et al. 1967)

These critiques demonstrate why it is not possible to extrapolate clear conclusions from these older studies about the safety and efficacy of LSD for any particular disorder. Instead, the data from these studies suggest possible psychiatric applications of hallucinogens, which may produce hypotheses that can be subjected to modern scientific evaluation through appropriate regulatory oversight. Such clinical studies have begun, but most of them are still in the small-scale, pilot study phase.

There is a common narrative among those who follow the history of psychedelic research that all clinical studies in the USA with this class of drugs terminated in 1976 and did not recur again until Rick Strassman began his dimethyltryptamine (DMT) clinical investigations in 1990. Although it is true that human hallucinogen research in the USA decreased dramatically after the 1960s, Yensen and Dryer (1992) report that investigators who had been associated with Spring Grove (by then renamed the Maryland Psychiatric Research Center) continued to administer LSD to patients with anxiety and depressive disorders under an IND until 1987.

So what brought about the severe reduction in hallucinogen studies in humans in the 1960s and 1970s? Surely the societal impact of the recreational use of LSD played a role, in terms of how Sandoz, the government, and even researchers distanced themselves from the bad perceptions associated by some with hallucinogens. But as this paper details, the inability of

researchers to comply with the new regulations often prevented study initiation. It is also likely that other regulatory issues also played a critical role.

FDA had strongly encouraged Sandoz in the 1950s "to think seriously about submitting [an NDA] as soon as possible" (Goddard 1966). By 1965, FDA's Kelsey fretted that clinical investigations with LSD "could not go on indefinitely without some attempt at obtaining an approved NDA" (Kelsey et al. 1965). Otherwise, the experimental drug effectively would be available to research psychiatrists as if it were a legally marketed drug, which is exactly what the 1962 Amendments sought to curtail. FDA proposed that they might consider giving an "effective NDA under very restrictive labeling", but Sandoz rejected the idea, stating that they were not considering the submission of any NDA (Kelsey et al. 1965). No other drug company stepped forward to take up the task of drug development for LSD, so the clinical studies conducted with the drug remained small and inconclusive (as is the case for any investigator-led drug study). This contributed to NIMH closing down their intramural (in-house) human research with LSD in 1968 (Oakley and Ksir 1999).

Then, in 1970, the U.S. Congress placed LSD into Schedule I of the CSA, indicating that the drug had high abuse potential and no currently accepted medical use, except for research. This created additional requirements for researchers who wished to conduct clinical studies with LSD, including the need to obtain a Schedule I license from DEA for each individual study. Under the CSA, the protocols and investigator/study site adequacy for these studies were evaluated not only by DEA, but by FDA, prior to the approval of the license (and separate from the IND system). Since DEA had no mandated time frame for responding to an applicant, a study could be in limbo for a long duration with little ability to prompt a response. Similarly, if FDA refused to let a clinical study with LSD proceed within the 30-day clock after initial submission of an IND, there was no mandated time frame with which FDA needed to resolve these concerns after an applicant provided additional information. Thus, the slow review time of INDs and Schedule I licenses by government agencies could prevent the initiation of a human study with LSD for long periods of time. Even though some clinical research with LSD was still proceeding, other tenacious researchers were surely frustrated by the time lag, which likely led to a decrease in the number of laboratories willing to engage in the regulatory endeavor.

On top of this, access to LSD was still largely limited to those laboratories that had successfully received funding from an NIMH grant after competing with other proposals for the experimental treatment of psychological disorders. By 1973, NIMH had spent 20 years and up to $7.5 million funding research with 2500 individuals who participated as subjects in 116 clinical studies with LSD (Asher 1975; Pollan 2015). However, NIMH had little to show for their two decades of investment in terms of progress towards an approved drug product. This was because large-scale Phase 2 and 3 studies demonstrating safety and efficacy had not been conducted with LSD, which meant there were no data to submit in an NDA—or a sponsor to submit it.

Then, in July 1975, NIMH abruptly announced that it was terminating all extramural (academic/medical center) funding of clinical studies with LSD. The timing of this came just weeks after the *Washington Post* and *New York Times* had broken a major story: military and intelligence agencies had been surreptitiously involved for 20 years in administering LSD and other psychoactive drugs to military personnel and civilians under the MKULTRA program, often by funding academic researchers. FDA had even waived the requirement for the military to conduct their drug studies under an IND (Ruskin 1965), which freed researchers from having to obtain informed consent, raising serious ethical issues. Thus, it is likely that NIMH sought to rapidly distance itself from the negative press by pulling out of the LSD clinical studies that had failed to produce a marketed medication to treat psychiatric illness. As the NIMH Research Task Force stated in 1975, "Attempts to use [LSD]... as an adjunct to traditional psychotherapy or as a special type of psychotherapeutic intervention have not clearly defined a therapeutic use" (Segal 1975).

Some 30 years later, NIMH (and NIDA) resumed funding clinical research with hallucinogens such as psilocybin, MDMA, and ketamine. In 2015, former NIMH Director Tom Insel said, "NIMH is not opposed to work with psychedelics, but I doubt we would make a major investment" because "it would be very difficult to get a pharmaceutical company interested in developing [them], since [they] cannot be patented" (Pollan 2015). As reported in the federal website ClinicalTrials.gov, most current studies with hallucinogens are small-scale Phase 1 or Phase 2 pilot studies. These studies may lay the foundation for future large-scale Phase 2 and 3 studies to demonstrate safety and efficacy of a drug for a specific medical indication. As pilot investigations, these modern human studies are similar to the those in the 1960s—except that they fully comply with appropriate regulations, ethics, and scientific standards for validity.

The history of human research with hallucinogens is still unfolding, nearly a century after it began. This paper contributes a new dimension to other fine reviews of this history (Campbell and Stark 2015; Carhart-Harris and Goodwin 2017; Doblin 2001; Grob 1998; Hagenbach and Werthmuller 2011; Lee and Shlain 1985; Mangini 1998; Neill 1987; Novak 2004; Oram 2014, 2016; Pollan 2015; Walsh and Grob 2005; Yensen and Dryer 1992) by providing specific regulatory reasons why LSD research diminished and by systematically focusing on the degree to which researchers conducting studies with LSD in the 1960s complied with (or struggled with) FDA regulations that protect patients and good science.

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Compliance with ethical standards

Disclaimer This paper reflects the views of the author and does not necessarily represent those of FDA.

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