

Agency Guidance Snapshot: Psychedelic Drugs: Considerations for Clinical Investigations - Guidance for Industry (*Draft Guidance*)

The Yale Human Research Protection Program (HRPP) has launched the “*Agency Guidance Snapshot*” series. The purpose of the Agency Guidance Snapshots is to highlight recent agency guidance from the Food and Drug Administration (FDA)¹, Office for Human Research Protections (OHRP), and other federal agencies that specifically impacts Yale University and affiliate stakeholders who conduct or oversee *human subjects research*.

Please Note: Yale University does not expect any immediate changes to policies due to this guidance; however, this guidance will be taken into consideration as policies and procedures are reviewed and revised in the future. Yale University may have additional requirements related to the topics covered in this guidance. For more information, please refer to the following Yale University Human Research Protection Program (HRPP) documents located on the HRPP website ([Policies, Procedures, Guidance, and Related Documents](#)) and in the Yale HRPP IRES-IRB Library ([IRES IRB LOGIN](#)): 1) [Yale HRPP Policy and Standard Operating Procedure Manual](#); 2) [Yale HRPP Investigator Manual](#); 3) [Yale IRB Members and Chairs Manual](#); and 4) [HRPP Supplemental Guidance Manual](#). Please also refer to [University Policies & Procedures](#) and policies published by the various Yale University schools and departments.

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Hyperlink to Document:	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/psychedelic-drugs-considerations-clinical-investigations

Overview of Guidance Document:

The U.S. Food and Drug Administration (FDA or Agency) is issuing this guidance to provide general considerations to sponsors (including sponsor-investigators) developing psychedelic drugs for treatment of medical conditions (e.g., psychiatric disorders, substance use disorders). For the purposes of this guidance, the term *psychedelic* is used as shorthand to include *classic psychedelics*, typically understood to be 5-HT₂ agonists such as psilocybin and lysergic acid diethylamide (LSD), as well as *entactogens* or *empathogens* such as methylenedioxymethamphetamine (MDMA).

This guidance applies to clinical trials that will be conducted under an investigational new drug application (IND), including such clinical trials (e.g., research or academic studies) that are not intended to support

¹ FDA Guidance documents represent the Agency's current thinking on a particular subject. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

marketing applications. The principles in this guidance are intended to support the ethical conduct of clinical trials as well as to ensure the integrity of the trial and the reliability of the results.

Background

In recent years, interest in the therapeutic potential of psychedelic drugs has been increasing. Psychedelic drug development programs are subject to the same regulations and same evidentiary standards for approval as other drug development programs. However, designing clinical studies to evaluate the safety and effectiveness of these compounds presents a number of unique challenges. Psychedelic drugs can cause intense perceptual disturbances and alterations in consciousness that can last for several hours. Some drug development programs incorporate a psychological or behavioral intervention. Investigators hypothesize that psychedelic drugs have both rapid-onset and long-term benefits after only one or a few doses. These and other unusual characteristics should be considered when designing clinical studies so that the results of those studies can be interpretable.

The interest of the FDA in psychedelic drug development stems from the recognition of the potential therapeutic benefits of these substances, the need for new treatment modalities for mental health conditions, and a shifting societal and legal landscape. Through regulatory oversight and guidance, the FDA aims to balance the promise of psychedelic therapies with the necessity for rigorous scientific evaluation and risk mitigation to ensure public safety and health.

Key Points for Sponsors (including Sponsor-Investigators), and IRB/HRPP Staff, Chairs, & Members:

The FDA's guidance provides foundational constructs that all sponsors, including academic sponsor-investigators, studying the therapeutic potential of psychedelic drugs should consider. Sponsors may also request meetings with FDA for advice on a specific drug development program.

Due to the unique nature of psychedelic drugs altering perception and consciousness, meticulous and reflective clinical study designs are essential to accurately interpret results and overcome inherent challenges. There is growing evidence that these substances can help alleviate symptoms of PTSD, depression, substance-use disorders, and anxiety. Research studies are underway to examine the impact of psychedelics for treatments of neurological conditions, as well, such as migraines.

Because of the potential for abuse of these drugs, the agency stresses the need for careful consideration and putting sufficient safety measures in place for preventing misuse throughout clinical development.

The draft guidance also addresses the role of psychotherapy in psychedelic drug development, considerations for safety monitoring and the importance of characterizing dose-response and the durability of any treatment effect.

General considerations for drug development programs evaluating the therapeutic potential of psychedelic drugs, by discipline, follow.

Chemistry, Manufacturing, and Controls

Sponsors must provide sufficient chemistry, manufacturing, and controls information to ensure proper identification, quality, purity, and strength of the investigational drug substance and drug product. This is true for all phases of clinical trials.

Drugs must be manufactured in compliance with current good manufacturing practice (CGMP) under section 501(a)(2)(b) of the Federal Food, Drug, and Cosmetic Act. For most drug products manufactured in support of phase 1 studies, manufacturers should follow the recommendations in the guidance for industry, *CGMP for Phase 1 Investigational Drugs* (July 2008). Certain drug products manufactured in support of phase 1 studies and drug products manufactured in support of phase 2 studies and beyond must comply with applicable CGMP regulations in 21 CFR part 211. Studies in which subjects are enrolled to measure the effectiveness of a drug for a particular indication or indications are generally considered phase 2 studies; therefore, the drug product used in those phase 2 studies must be manufactured in accordance with CGMP requirements.

Investigators and sponsors are encouraged to refer to the guidance for industry *INDs for Phase 2 and 3 Studies; Chemistry, Manufacturing, and Controls Information* (May 2003) and the guidance for industry *Content and Format of INDs for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products* (October 2000).

Nonclinical

It may be reasonable for clinical studies with certain psychedelic drugs to be initiated under an IND in the absence of the typical animal toxicology testing when extensive human exposure and information are available from previously conducted clinical studies and no serious safety concerns were identified.

An IND must include adequate information about pharmacological and toxicological studies of the drug on the basis of which the sponsor has concluded it is reasonably safe to conduct the proposed clinical investigations. Therefore, psychedelic drugs without a history of adequate clinical exposure should not be tested in humans until safety has been established in nonclinical studies.

Clinical Pharmacology

Pharmacokinetics and/or pharmacodynamics of psychedelic drugs should be adequately characterized both in vitro and in vivo. Sponsors should evaluate potential drug-drug and drug-disease interactions to inform inclusion and exclusion criteria and prohibited concomitant medications for clinical studies and to inform potential labeling. Sponsors should evaluate the impact of diet (e.g., high fat meal) and drug-drug interactions. Because of the known cardiac risks associated with the use of psychedelics, researchers must closely monitor pharmacodynamic interactions with selective serotonin reuptake inhibitors (SSRIs) and other antidepressants.

Abuse Potential Assessment

The assessment of the abuse potential of a drug product under development is generally conducted as a component of its safety evaluation. Psychedelic drugs act on the central nervous system, produce psychoactive effects (e.g., mood or cognitive changes, hallucinations), and need to be evaluated for abuse potential during drug development. Data from the abuse potential assessment and a proposal for drug scheduling under the Controlled Substances Act is required to be included in a new drug application

submission. For psychedelic drugs that are Schedule I controlled substances, activities associated with investigations under an IND must comply with the applicable Drug Enforcement Administration (DEA) regulations for research, manufacturing, importation/exportation, handling, and storage requirements for a Schedule I drug.

For some psychedelic drugs that are Schedule I controlled substances, there have been numerous investigations of these drugs, as documented in the published scientific literature. When appropriate, sponsors should propose the use of scientifically valid, published investigations to support the abuse potential assessment.

An evaluation of psychedelic responses that occur during clinical studies should be obtained through the inclusion of validated subjective scales and through monitoring abuse-related adverse events (AEs), such as euphoria, hallucinations, stimulation, and emotional lability. Abuse-related AEs are monitored and reported as a safety concern even if they are hypothesized to be associated with the therapeutic response. Thus, for psychedelic drugs, investigators and session monitors should be trained to record all abuse-related AEs, including psychedelic ones.

An assessment of the potential for physical dependence with a psychedelic drug may be appropriate as part of the abuse potential assessment depending on the proposed conditions of use for which the drug is being studied (e.g., acute intermittent use versus prolonged continuous use).

Clinical Study

Use of Placebo

The guidance addresses the challenge of designing an adequate and well-controlled (AWC) clinical study, considering the intense perceptual effects of active ingredients versus placebo. The guidance offers recommendations to address this, including the use of an inert placebo or other psychoactive drugs that mimic some aspects of the psychedelic experience.

Co-administered Psychotherapy

Many of the psychedelic drug development programs involve administering the investigational drug and then engaging in psychological support or psychotherapy either while the subject is experiencing the acute effects of the drug or in a subsequent session. This additional variable both complicates the assessment of effectiveness and presents a challenge for any future product labeling. Sponsors should plan to justify the inclusion of a psychotherapy component and describe any trial design elements intended to reduce potential bias or to quantify the contribution of psychotherapy to the overall treatment effect. A factorial design may be useful for characterizing the separate contributions of drug and psychotherapy to any observed treatment response.

Safety Monitoring

To address the vulnerable state that subjects receiving active treatment with psychedelic drugs remain in (as long as 12 hours), safety monitoring should include observation by two monitors for the duration of the treatment session. The lead monitor should be a licensed healthcare provider with graduate-level professional training and clinical experience in psychotherapy.

Informed Consent

The informed consent should clearly describe that subjects may experience changes in perception, cognition, and judgment that persist for many hours, as well as increased vulnerability and suggestibility during the treatment session.

For more related information, please see the following links to additional resources:

- [FDA Guidance Documents](#)
- [JAMA: FDA Proposes First Guidance for Researchers Studying Psychedelics](#)
- [How Should the FDA Evaluate Psychedelic Medicine? \(10.1056/NEJMp2308940\)](#)
- [Ropes & Gray: Controlling Opinions: Introducing Ropes & Gray's Controlled Substances Compliance Update](#)
- [WCG Talks Trials: Delve into the World of Psychedelic Research and Ethical Inquiry](#)

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