
Psychedelic Drugs: Considerations for Clinical Investigations Guidance for Industry

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**July 2026
Clinical/Medical**

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Psychedelic Drugs: Considerations for Clinical Investigations Guidance for Industry¹

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The U.S. Food and Drug Administration (FDA or Agency) is issuing this guidance to provide general considerations to sponsors developing psychedelic drugs for the treatment of medical conditions (e.g., psychiatric disorders, substance use disorders). For the purposes of this guidance, the term *psychedelic drug* is used as shorthand to include *classic psychedelics*, typically understood to be 5-HT_{2A} receptor agonists such as psilocybin and lysergic acid diethylamide (LSD), as well as *entactogens* or *empathogens* such as 3,4-methylenedioxymethamphetamine (MDMA). The regulatory concepts discussed in this guidance may also apply to other related products that can cause perceptual disturbances and alterations in consciousness.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In recent years, interest in the therapeutic potential of psychedelic drugs has been increasing. Drug development programs for psychedelic drugs 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 products presents a number of unique challenges. Psychedelic drugs can cause intense perceptual disturbances and alterations in consciousness that can last for several hours or days. 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.

¹ This guidance has been prepared by the Division of Psychiatry in the Center for Drug Evaluation and Research at the Food and Drug Administration.

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These and other unusual characteristics should be considered when designing clinical studies so that the results of those studies can provide reliable data on efficacy and safety.

Because this is an emerging area of drug development, there is limited experience with the design of drug development programs that may support approval of psychedelic drugs. Rather than providing specific recommendations on study design, this guidance will present foundational constructs that all sponsors studying the therapeutic potential of psychedelic drugs, including sponsors without commercial drug development as primary interest (e.g., academic researchers), should consider. Sponsors are encouraged to request meetings with FDA for advice on a specific drug development program.²

This guidance applies to clinical trials that will be conducted under an investigational new drug application (IND), including clinical trials conducted under a research IND that are not intended to support 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.

III. DISCUSSION

Below, we outline general considerations, by discipline, for drug development programs evaluating the therapeutic potential of psychedelic drugs. The Agency is open to discussing various approaches to address these considerations; sponsors should engage divisions early in the drug development process.

A. 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.³ This is true for all phases of clinical trials.

- Chemistry data submitted by a sponsor to FDA may be proprietary. In general, sponsors interested in conducting a clinical investigation with psychedelic drugs under an IND must either submit their own information or incorporate information previously submitted by a person other than the sponsor when the sponsor has a written statement that authorizes the right of reference for such information.⁴

² See the draft guidance for industry *Formal Meetings Between the FDA and Sponsor or Applicants of PDUFA Products* (September 2023). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

³ See 21 CFR 312.23(a)(7).

⁴ See 21 CFR 312.23(b).

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- If using plant material, algae, macroscopic fungi, or a combination of these, the investigational product may be considered a botanical, as that term is defined in the guidance for industry *Botanical Drug Development* (December 2016).⁵
- Although some psychedelic drugs are derived from plants or fungi, drug products that are genetically modified; produced by fermentation of yeast, bacteria, or plant cells; or highly purified substances from naturally occurring sources are not considered botanicals for purposes of this document and the guidance for industry *Botanical Drug Development*.
- 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 (FD&C 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.^{6,7} If the drug under investigation is part of a combination product, the applicant may be subject to additional regulations such as 21 CFR parts 820 and 4.⁸ Initial 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;⁹ therefore, the drug product used in those phase 2 studies must be manufactured in accordance with CGMP requirements.¹⁰ Each phase of the investigation requires sufficient information to ensure identification, quality, purity, and strength of the investigational drug substance and drug product.¹¹ Investigators and sponsors are encouraged to refer to the guidances for industry *INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information* (May 2003) and *Content and Format of INDs for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products* (October 2000).¹²

⁵ We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

⁶ See 21 CFR 210.2(c).

⁷ See 21 CFR part 211.

⁸ See 21 CFR part 4 and 21 CFR part 820.

⁹ See 21 CFR 312.21(b).

¹⁰ See 21 CFR 210.2(c).

¹¹ See 21 CFR 312.23(a)(7)(i).

¹² For more general information about the IND process, see <https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application>.

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B. Nonclinical

The nonclinical program for psychedelic drugs should follow recommendations outlined in the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010).¹³ However, the following considerations may be unique to psychedelic drugs given that some development programs may rely on prior human experience to support safety of an initial IND:

- 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.¹⁴ Therefore, psychedelic drugs without a history of adequate clinical exposure should not be tested in humans until safety has been established in nonclinical studies. The FDA encourages submission of data from new approach methodologies where appropriate as outlined in the draft guidance for industry *General Considerations for the Use of New Approach Methodologies in Drug Development* (March 2026).¹⁵
- When adequate human exposure and information are available for a given psychedelic drug from previously conducted clinical studies and no serious safety concerns were identified, it may be reasonable for clinical studies to be initiated under an IND in the absence of standard animal toxicology testing.¹⁶
- The need for and type of nonclinical studies to support further drug development after initial clinical studies will be determined by the extent of available nonclinical and clinical safety information. Sponsors should plan to conduct nonclinical studies to support further drug development after initiation of the IND unless the sponsor provides adequate data from the published scientific and medical literature.¹⁷
- If repeat dosing is expected, nonclinical studies to support chronic or repeated intermittent dosing should be provided.¹⁸ Sponsors should determine the most appropriate dosing paradigm (e.g., dosing intervals) in the repeat-dose toxicity studies to

¹³ We encourage the use of new approach methodologies in place of animal testing where appropriate.

¹⁴ 21 CFR 312.23(a)(8).

¹⁵ When final, this guidance will represent the FDA's current thinking on this topic.

¹⁶ See 21 CFR 312, 314, and 601 (for information about the requirements for an IND, a new drug application, or a biologics license application).

¹⁷ See 21 CFR 312, 314, and 601 (for information about the requirements for an IND, a new drug application, or a biologics license application).

¹⁸ See 21 CFR 312.23(a)(8) (providing information on requirements in INDs. The regulation specifies that "[t]he kind, duration, and scope of animal and other tests required [to conduct the proposed clinical investigation] varies with the duration and nature of the proposed clinical investigations.").

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support their intended clinical studies. The number and types of nonclinical studies to support approval of a marketing application will largely depend on the treatment paradigm.

- For psychedelic drugs with serotonin (5-HT) activity, the 5-HT_{2B} receptor subtype has been linked to heart valvulopathy in humans;¹⁹ therefore, sponsors should assess functional activity at the 5-HT_{2B} receptor subtype. If a psychedelic drug is shown to be an agonist at 5-HT_{2B} receptors, a thorough microscopic evaluation of the heart should be conducted to assess for potential heart valve thickening in both rodent and nonrodent repeat-dose toxicity studies, including sectioning of all heart valves. We encourage the consideration of nonanimal-based evaluation of the risk of valvulopathy (e.g., validated quantitative structure–activity relationship (QSAR) models), as supportive or complementary data, provided that adequate validation information on the novel approaches used are included with the application.

C. Clinical Pharmacology

Pharmacokinetics and/or pharmacodynamics of psychedelic drugs should be adequately characterized both in vitro and in vivo. Sponsors should also consider the potential impact of the following clinical pharmacology aspects when developing psychedelic drugs:

- Sponsors should evaluate the effect of a high-fat meal on the pharmacokinetics of an oral psychedelic drug early in development to inform clinical study design and potential labeling.
- Sponsors should evaluate potential impact of intrinsic and other extrinsic factors on the pharmacokinetics of the psychedelic drug to inform inclusion and exclusion criteria, prohibited concomitant medications for clinical studies, and potential labeling.^{20,21}
- Long-term exposure to drugs that have 5-HT_{2B} agonism may induce cardiac valve stiffening. Currently, FDA recommends that sponsors exclude subjects with preexisting valvulopathy or pulmonary hypertension from multiple-dose studies of drugs with this mechanism until this risk can be better characterized.
- Sponsors should consider the impact of pharmacodynamic and pharmacokinetic interactions on interpretability of efficacy data and on subject safety. Although safety risks should be mitigated by prohibiting certain concomitant medications, interpretability concerns for other medications may be managed by a variety of means (e.g., excluding

¹⁹ Hutcheson, JD, V Setola, BL Roth, and WD Merryman, 2011, Serotonin Receptors and Heart Valve Disease – It Was Meant 2B, *Pharmacol Ther*, 132(2):146–157.

²⁰ See the ICH guidance for industry *M12 Drug Interaction Studies* (August 2024).

²¹ See the guidance for industry *Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications* (March 2023).

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concomitant administration, stratifying analyses by class of comedication). Although more research is needed, potential interactions to consider include, but are not limited to, the following:

- Use of selective serotonin reuptake inhibitors, serotonin/norepinephrine reuptake inhibitors, or monoamine oxidase inhibitors for 3 weeks or more may reduce the subjective effects of psychedelic drugs.²²
- Use of tricyclic antidepressants or lithium for 3 weeks or more may potentiate the subjective effects of psychedelic drugs, creating a potential psychiatric safety concern. Use of selective serotonin reuptake inhibitors, serotonin/norepinephrine reuptake inhibitors, or monoamine oxidase inhibitors for less than 3 weeks may also potentiate the subjective effects of psychedelic drugs.²³
- Use of monoamine oxidase inhibitors in combination with MDMA or other amphetamine-based psychedelic drugs can produce a life-threatening hypertensive crisis.
- Sponsors should evaluate the pharmacokinetics of a psychedelic drug in patients with impaired renal function and patients with impaired hepatic function to provide dose adjustment recommendations and inform labeling.^{24,25}

D. 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. New drug products that are assessed for abuse potential include those that are active on the central nervous system. For general information on how to conduct the abuse potential evaluation, including recommended methodologies and what studies should be included as part of the new drug application submission, see the guidance for industry *Assessment of Abuse Potential of Drugs* (January 2017). The following considerations apply for psychedelic drugs being developed as new drug products:

- 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

²² Bonson KR, JW Buckholtz, DL Murphy, 1996, Chronic Administration of Serotonergic Antidepressants Attenuates the Subjective Effects of LSD in Humans, *Neuropsychopharmacology*, 14:425–436.

²³ Bonson KR and DL Murphy, 1996, Alterations in Responses to LSD in Humans Associated With Chronic Administration of Tricyclic Antidepressants, Monoamine Oxidase Inhibitors or Lithium, *Behav Brain Res*, 3(1-2):229–233.

²⁴ See the guidance for industry *Pharmacokinetics in Patients with Impaired Hepatic Function: Study, Design, Data Analysis, and Impact on Dosing and Labeling* (May 2003).

²⁵ See the guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function – Study, Design, Data Analysis, and Impact on Dosing* (March 2024).

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during drug development.²⁶ Data from the abuse potential assessment and a proposal for drug scheduling under the Controlled Substances Act are required to be included in a new drug application submission.²⁷ Many psychedelic drugs are Schedule I substances under the Controlled Substances Act²⁸ because they have a high potential for abuse and do not have a currently accepted medical use in treatment in the United States.²⁹ Should a psychedelic drug that is a Schedule I controlled substance receive FDA approval as a drug product, the abuse potential assessment would assist in determining an appropriate rescheduling action under the Controlled Substances Act.

- For psychedelic drugs that are Schedule I controlled substances, activities associated with investigations under an IND must comply with the Controlled Substances Act, and applicable implementing regulations adopted by the Drug Enforcement Administration (DEA), relating to research, manufacturing, importation/exportation, handling, and storage requirements for a Schedule I drug.³⁰ Sponsors may contact DEA to discuss and ensure compliance with all applicable DEA requirements.
- Some psychedelic drugs have already been well-characterized in preclinical investigations published in the scientific literature. The need for a sponsor to conduct new abuse-related animal studies (such as drug discrimination) with a specific psychedelic drug will depend on an FDA evaluation of the design and quality of published animal studies that will be referenced by the sponsor. Self-administration and conditioned place preference studies are not usually required for psychedelic drugs because they typically do not produce positive signals in those studies.
- A human abuse potential study should generally be conducted when a drug has shown abuse-related signals in animal and/or human studies. However, a human abuse potential study may not be scientifically necessary for certain psychedelic drugs to support the abuse potential assessment in a new drug application when the subjective effects predictive of abuse are well-characterized from extensive clinical studies and robust epidemiological data exist to demonstrate that individuals are using the psychedelic drug for abuse purposes. Sponsors are encouraged to reach out to FDA during the IND stage if they believe there is sufficient existing data that the human abuse potential is already well-characterized.

²⁶ See 21 CFR 314.50(d)(5)(vii).

²⁷ Ibid.

²⁸ See 21 CFR 1308.11.

²⁹ Schedule I drugs and substances, as defined under the Controlled Substances Act, are those with high potential for abuse and have no currently accepted medical use in treatment in the United States. Once a drug is approved by FDA, and therefore found to have a currently accepted medical use, it will be placed within schedule II-V as determined by the relative abuse potential of the drug and the relative degree to which it induces psychological or physical dependence (21 U.S.C. 812(b)).

³⁰ See 21 CFR part 1301.

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- An adverse event (AE) for purposes of IND safety reporting means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.³¹ Some expected psychoactive effects such as euphoria, hallucinations and other perceptual distortions, and alterations in cognition should also be recorded as AEs for psychedelic drugs given their association with abuse potential, even if subjects do not describe these effects as adverse.
- An evaluation of psychoactive effects that occur during clinical studies should be obtained through the inclusion of validated clinical outcome assessments and through monitoring AEs associated with abuse potential. AEs associated with abuse potential are monitored and reported as a safety concern even if they are hypothesized to be associated with the therapeutic response.³² Thus, for psychedelic drugs, investigators and session monitors should be trained to identify and document all central nervous system effects, including the expected psychoactive effects. For more information about procedures for monitoring and assessing AEs associated with abuse potential, refer to section V.B of the guidance for industry *Assessment of Abuse Potential of Drugs*.
- 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., repeated intermittent use versus prolonged continuous use).
- It is generally recommended that abuse-related studies should be conducted only after the final therapeutic dose range is determined, which typically occurs when phase 2 clinical studies are completed. Sponsors or investigators should submit proposed protocols to the Agency for review and comment before conducting these abuse-related studies.
- An evaluation of available epidemiological data is another critical component of an abuse potential assessment for a psychedelic drug already known to be used for recreational or federally unapproved medical purposes. Thus, applicants should provide as part of their new drug application an analysis of the scope of abuse and associated harms, based on a systematic review of the published literature and other available epidemiological data sources.
- Sponsors or investigators may also submit computer modeling of abuse potential based on chemical structure/molecular target/mechanism of action to the Agency for review.³³
- Sponsors are encouraged to discuss their plans for an abuse potential assessment with FDA early in the IND stage of drug development and request (through the primary

³¹ 21 CFR 312.32(a).

³² 21 CFR 312.32(c).

³³ See the draft guidance for industry *General Considerations for the Use of New Approach Methodologies in Drug Development*.

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review division) review and comment on these plans from the Controlled Substance Staff in the Center for Drug Evaluation and Research.

E. Clinical

To establish a drug's effectiveness, it is essential to distinguish the effect of the drug "from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation."³⁴ This is the basis for the statutory requirement that a new drug approval be based on adequate and well-controlled investigation(s), as well as the basis for FDA's regulations describing the characteristics of an adequate and well-controlled investigation.³⁵ Designing an adequate and well-controlled clinical investigation of psychedelic drugs can be challenging for sponsors given the often intense perceptual changes induced by the drugs. This increases the potential for bias due to functional unblinding of patients, therapists, monitors, or raters. Functional unblinding can lead to expectation bias in the patients who experience perceptual disturbances, or in those who observe them, which may lead to an expectation that the participant will experience clinical benefit; alternatively, those who receive a placebo and do not experience or observe a perceptual change may expect that the participant will not benefit.

1. Trial Design

- Given concerns for functional unblinding, the use of a traditional placebo as a control can be problematic for assessing efficacy even though it provides better contextualization for safety findings. Alternatives to an inert placebo (e.g., lower doses of a psychedelic, other psychoactive drugs that mimic some aspects of the subjective experience associated with psychedelic drugs) may be considered as well. The Agency encourages the consideration of innovative approaches for control groups. In general, controls should be closely matched to the treatment group for clinically relevant variables and clinical care. Study results should be strongly persuasive and robust across study endpoints to overcome biases that may be introduced by functional unblinding.
- Clinical trial design proposals should be discussed with the review division before the initiation of a study.
- There are a number of approaches that can help minimize bias on the part of the subjects, observers, and analysts of the data that may be applicable to trials with psychedelic drugs.
 - Sponsors should incorporate the use of central raters blinded to treatment allocation and visit number.
 - For randomized clinical trials, the use of a blinding questionnaire for both subjects and investigators/observers/raters (i.e., asking each whether they think the subject received active drug or placebo with a Likert scale to characterize certainty of the

³⁴ See section 505(d) of the FD&C Act; 21 CFR 314.126.

³⁵ See 21 CFR 314.126(b)(2).

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guess) can be helpful to evaluate the impact of functional unblinding. This may also be helpful in a trial using a range of doses.

- An expectancy evaluation questionnaire (i.e., assessing subjects' expectations about potential drug effects) pre-randomization and at the end of treatment to improve data interpretability despite functional unblinding should be considered.
- Although it has been hypothesized that one or a few doses of a psychedelic drug will produce lasting therapeutic benefit, many of the conditions that these drugs are purported to treat typically persist for months or years. Therefore, sponsors should plan to evaluate the durability of response for their drug product and the safety and efficacy of repeat dosing.
 - Before an initial application for a product intended for the treatment of a chronic illness such as post-traumatic stress disorder or major depressive disorder, sponsors should evaluate with a double-blind design the effect of treatment at 12 weeks.
 - Sponsors should continue to follow subjects beyond the Week 12 endpoint to monitor for symptom recurrence or, potentially, the need for repeat dosing.
 - The most informative clinical trial design would incorporate blinded long-term follow-up (typically 12 months) with prespecified criteria for retreatment. These criteria should take into account symptom ratings as well as whether the participant seeks additional treatment outside the study.
 - If data suggest that readministration on a regularly scheduled basis is warranted, the recommended interdose interval for maintenance of effect should be studied; it may be reasonable to conduct studies of specific maintenance treatment paradigms in the postmarketing period.
- Sponsors should plan to characterize the dose-response relationship for both safety and efficacy early in the drug development program.
- Complementary trial designs across phases 2 and 3 could address different challenges in psychedelic drug development. For example, a trial using a low, middle, and high dose without a placebo could be paired with a placebo-controlled trial. The trial without a placebo could provide information about dose-response with less risk of functional unblinding. Although the placebo-controlled trial may raise concerns for bias related to functional unblinding, it will allow for better characterization of safety signals.
- The clinical trial population should be reasonably representative of the population in which the product is intended to be used; however, enrolling individuals with prior psychedelic drug exposure raises the possibility of expectation bias given that participants who have prior experience with psychedelic drugs are more likely to recognize their subjective effects (i.e., leading to functional unblinding) and anticipate a treatment benefit. It is reasonable to include some individuals with prior experience with

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psychedelic drugs; however, they should not be overrepresented in the trial population and randomization should be stratified based on prior psychedelic drug usage.

- Although the FDA does not address inclusion and exclusion criteria in this guidance, we advise that the included population be representative of the population intended to receive the treatment. Trials should not unnecessarily exclude subjects who have certain health characteristics (e.g., age, treatment history, concurrent treatments, pregnancy) if these groups are intended to receive the treatment post-approval, but they should be appropriately stratified. Excluded populations may not be described in the approved indication in prescribing information.³⁶
- Many of the psychedelic drug development programs involve administration of the investigational product and engaging in psychological support or psychotherapy either while the subject is experiencing the acute effects of the drug or in a separate session. This additional variable both complicates the assessment of effectiveness and presents a challenge for any future product labeling.
 - As of the publication date of this guidance, the contribution of the psychotherapy component to any efficacy observed with psychedelic drug treatment has not been characterized. A factorial design may be useful for characterizing the separate contributions of drug and psychotherapy to any observed treatment response.
 - The therapist monitoring the session can usually deduce the treatment assignment by observing the subject's behavior; thus, their knowledge of the treatment could bias the delivery of subsequent therapy. One option for managing this bias within the clinical trial could be to ensure that the in-session monitor is not involved in post-session psychotherapy.
 - Sponsors should describe their planned treatment paradigm, including whether drug administration will be paired with psychological support or psychotherapy, and provide a rationale for the chosen model. Sponsors should also describe any trial design elements intended to reduce potential bias or to quantify the contribution of psychotherapy to the overall treatment effect. The treatment paradigm used in the trials may be described in product labeling.

2. Safety Considerations

FDA may place a study under an IND on clinical hold if it finds, among other reasons, that human subjects are or would be exposed to an unreasonable and significant risk of illness or injury.³⁷ Subjects receiving active treatment with psychedelic drugs may remain in a vulnerable state for several hours or longer. Given this concern, and so that subjects are not placed at an unreasonable and significant risk of illness or injury, the Agency expects safety monitoring to include the following:

³⁶ See generally 21 CFR 201.57(c)(2).

³⁷ 21 CFR 312.42.

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- Observation by two monitors for the duration of the treatment session.
 - A health care provider with graduate-level professional training and clinical experience in psychotherapy, licensed to practice independently, serving as the *lead* monitor.
 - An *assistant* monitor with a nursing or bachelor's degree and at least 1 year of clinical experience in a licensed mental health care setting.
- If the lead monitor is not a physician, availability of a licensed on-call physician able to reach the clinical site within 15 minutes in the event of a medical emergency.
- 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.
- The incidence, duration, and severity of all central nervous system effects, including expected psychedelic effects (e.g., euphoria, hallucinations and other perceptual distortions, alterations in cognition, and changes in mood) should be identified and documented throughout the session, regardless of whether the experience is characterized as positive, favorable, or neutral, or whether the effects align with what is expected from the investigational drug. It is important to characterize onset and resolution of psychedelic and other subjective effects.
- For drugs with a history of human use, sponsors should conduct a systematic review of the literature to identify AEs associated with recreational or unapproved use of the drug to identify potential safety issues. AEs known to occur in the context of illicit use should be treated as predefined adverse events of special interest and assessed systematically in the drug development program.
- Sponsors should plan to provide a quantitative and qualitative assessment of the drug effects, including effects on orientation to time and place, thought and perception, and subjective effects across time that could inform recommendations for monitoring, safety of discharge, and impact on driving. Sponsors should consider including a formal driving study in their drug development plan.³⁸
- For drugs that have been shown to have functional activity at the 5-HT_{2B} receptor, baseline and follow-up echocardiograms to assess valve structure and function and pulmonary artery pressures should be included in the study for drugs that are to be chronically administered. As of the publication of this guidance, the dosing paradigm for psychedelic drugs has yet to be established; therefore, it is not clear whether this advice

³⁸ See the guidance for industry *Evaluating Drug Effects on the Ability to Operate a Motor Vehicle* (November 2017).

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will be relevant to psychedelic drugs. Nonetheless, patients with preexisting valvulopathy or pulmonary hypertension should be excluded until the cardiac risk has been characterized. Recommendations for when and how to assess QT interval and blood pressure can be found in the guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October 2005) and the draft guidance for industry *Assessment of Pressor Effects of Drugs* (February 2022).³⁹

- Sponsors should address how AEs or serious risks are mitigated during the clinical studies and if similar strategies can or should be implemented postmarketing.
- Sponsors should consider risk mitigation strategies to mitigate the risk of nonmedical use, accidental exposure, and overdose for both patients and nonpatients. Sponsors should also consider if gaps exist in the health care system regarding safe use.⁴⁰
- Given the risks of alteration in mental status and/or impairment in judgement and decision-making following psychedelic drug administration, the Agency anticipates that additional assessments of safety may be needed in the postmarketing setting when a larger population will be exposed to these products. Sponsors should consider the potential need for a risk evaluation and mitigation strategy or additional safety studies that may be required in the postmarketing setting when preparing and submitting a marketing application.
- FDA may consider the public health effects of the drug as part of the overall benefit-risk assessment. Public health effects of the drug include its potential effect on risks that are related to nonmedical use, substance use disorder, accidental exposure, and overdose for patients and the broader population.

³⁹ When final, this guidance will represent the FDA's current thinking on this topic.

⁴⁰ See the draft guidance for industry *REMS Logic Model: A Framework to Link Program Design With Assessment* (May 2024). When final, this guidance will represent the FDA's current thinking on this topic.