Psychedelic Drugs: Considerations for Clinical Investigations

Guidance for Industry

DRAFT GUIDANCE

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

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Psychedelic Drugs: Considerations for Clinical Investigations Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 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).

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. 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.

[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.

Because this is an emerging area of drug development, there is limited experience as to the configuration of programs that may support approval of a psychedelic drug. Rather than providing specific recommendations on study design, this guidance will present 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.[2]

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 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 a psychedelic drug 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 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* (December 2017). 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).

- 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 compounds 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. 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] 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;[8] therefore, the drug product used in those phase 2 studies must be manufactured in accordance with CGMP requirements.[9] Each phase of the investigation requires sufficient information to ensure identification, purity, and strength of the investigational drug substance and drug product.[10] 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).[11]

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*

[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 312.21(b).

[9] See 21 CFR 210.2(c).

[10] See 21 CFR 312.23(a)(7)(i).

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

Trials and Marketing Authorization for Pharmaceuticals (January 2010).[12] However, the following considerations may be unique to psychedelic drugs.

- 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. Sponsors should plan to conduct nonclinical studies to support further drug development after initiation of the IND unless there are adequate data in the published scientific and medical literature.[13,14]

- 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.[15] Therefore, psychedelic drugs without a history of adequate clinical exposure should not be tested in humans until safety has been established in nonclinical studies.[16]

- Although current psychedelic drug development programs are exploring single-dose or intermittent-dose treatment paradigms, most of the conditions being studied to date in these programs are chronic. Nonclinical studies to support chronic or chronic-intermittent dosing should be provided if the treatment effect is not durable and repeat dosing is expected.[17] Sponsors should determine the most appropriate dosing paradigm (e.g., dosing intervals) for each animal species in the repeat-dose toxicity studies to support their intended clinical studies. The number and types of nonclinical studies to support approval of a marketing application will largely depend on treatment paradigm.

- Because psychedelic drugs have serotonin (5-HT) activity, a thorough evaluation of binding to 5-HT receptor subtypes should be conducted. Binding to the 5-HT2B receptor subtype has been linked to heart valvulopathy in humans; therefore, sponsors should assess functional activity at the 5-HT2B receptor subtype. If a psychedelic drug is shown to be an agonist at 5-HT2B receptors, a thorough microscopic evaluation of the heart

[12] We support the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if it they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

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

[14] See the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010).

[15] 21 CFR 312.23(a)(8).

[16] See the guidance for industry *Safety Testing of Drug Metabolites* (March 2020) and ICH M3(R2).

[17] 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").

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.

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 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 drug-drug and drug-disease interactions to inform inclusion and exclusion criteria and prohibited concomitant medications for clinical studies and to inform potential labeling.[18,19,20]

- Long-term exposure to 5-HT2B agonists 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.

- Known pharmacodynamic interactions to consider include the following:

  - Chronic use of selective serotonin reuptake inhibitors or monoamine oxidase inhibitors may reduce the effect of psychedelic drugs.

  - Chronic use of tricyclic antidepressants or lithium and acute use of selective serotonin reuptake inhibitors or monoamine oxidase inhibitors use may potentiate psychedelic effects.

- The dose-response relationship for most psychedelic drugs is poorly understood. Sponsors should take appropriate steps to characterize the dose-response relationship, both for efficacy and for safety.

[18] See the guidance for industry *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020).

[19] See the guidance for industry *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020).

[20] 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).

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. Drug products that are assessed for abuse potential include new molecular entities that are active on the central nervous system, as well as those products that contain drugs that are already controlled under the Controlled Substances Act.

- 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.[21] 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.[22] Many psychedelic drugs are Schedule I substances under the Controlled Substances Act[23] because they have high abuse potential and do not have a currently accepted medical use in the United States. 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 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* (2017).

- 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.[24] This requirement includes DEA registration of the investigator who intends to conduct research, per 21 U.S.C. 823(g) and the implementing regulation 21 CFR 1301.18. A Schedule I registration issued by DEA is required before the initiation of nonclinical and clinical studies. Authorization to conduct the research is required for each specific protocol and may need to be supplemented for amendments made to a protocol.[25] Sponsors should contact DEA to discuss and ensure compliance with all applicable DEA requirements.

- 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. For those psychedelic drugs that have not been well-characterized previously in preclinical and clinical studies,

[21] See 21 CFR 314.50(d)(5)(vii).

[22] Ibid.

[23] See 21 CFR 1308.11.

[24] See 21 CFR part 1301.

[25] 21 CFR 1301.18.

sponsors should conduct a full abuse potential assessment, as described in the guidance for industry *Assessment of Abuse Potential of Drugs*, before submission of a new drug application.

- 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.

- 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.[26] 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 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.[27] Thus, for psychedelic drugs, investigators and session monitors should be trained to record all abuse-related AEs, including psychedelic ones. The incidence of these abuse-related AEs in comparison to placebo or active control in studies should be reported by study, population, and dose and should be displayed in tabular format. Narratives describing these events should also be provided. Sponsors are encouraged to discuss their abuse-related AE monitoring plan early in development with the Controlled Substance Staff (through the primary review division). For more information about procedures for monitoring and assessing abuse-related AEs, 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., acute intermittent use versus prolonged continuous use).

- For all animal and human abuse potential and dependence-related studies that will contribute to the abuse potential assessment, it is generally recommended that these studies be conducted only after the therapeutic dose range is determined, which typically occurs when phase 2 clinical studies are completed. FDA recommends submitting proposed protocols to the Agency for review and comment before conducting these abuse-related studies.

[26] 21 CFR 312.32(a).

[27] 21 CFR 312.32(c).

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

E. Clinical

The substantial evidence standard for establishing effectiveness of psychedelic drugs is the same as it is for all other drugs.[28] However, the following considerations may be unique to psychedelic drugs.

- Adequate and well-controlled (AWC) clinical studies are generally required to meet the substantial evidence standard to establish effectiveness in a marketing application.[29] However, the characteristics of psychedelic drugs present challenges for sponsors in designing AWC clinical studies.

  - An AWC study uses a design that permits a valid comparison with a control to provide a quantitative assessment of a drug's effect.[30] In the context of psychedelic drug development, the use of a traditional placebo as a control can be problematic for assessing efficacy. Subjects receiving an active drug experience functional unblinding because of the intense perceptual disturbances that can develop; those who receive a placebo in the context of high expectancy may experience a *nocebo* effect (i.e., worsening symptoms as a result of knowing they did not get active treatment). However, an inactive control allows for better contextualization of any safety findings. Alternatives to an inert placebo (e.g., subperceptual doses of a psychedelic drug, other psychoactive drugs that mimic some aspects of the psychedelic experience) may be considered as well.

  - In an AWC study, adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data.[31] Sponsors should consider the use of video or central raters blinded to treatment allocation and visit number. The use of a blinding questionnaire for both subjects and investigators/raters can be helpful to evaluate the impact of functional unblinding.

  - 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 without the risk of

[28] See section 505(d) of the FD&C Act; see also the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic.

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

[30] See 21 CFR 314.126(b)(2).

[31] See 21 CFR 314.126(b)(5)

a nocebo effect. The placebo-controlled trial may raise concerns about functional unblinding but will allow for better characterization of safety signals.

- 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.

  - As of the publication date of this guidance, the contribution of the psychotherapy component to any efficacy observed with psychedelic treatment has not been characterized.

  - Psychotherapeutic interventions have the potential to increase expectancy and performance biases. 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.

  - The therapist monitoring the session can usually deduce the treatment assignment by observing the subject's behavior. Therefore, it is preferable that the in-session monitor is not involved in post-session psychotherapy because their knowledge of the treatment could bias the delivery of subsequent therapy.

- FDA may place a study under an IND under 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.[32] Subjects receiving active treatment with psychedelic drugs remain in a vulnerable state for as long as 12 hours. Given this concern, so that subjects are not placed at an unreasonable and significant risk of illness or injury, safety-monitoring should include the following:

  - Observation by two monitors for the duration of the treatment session

    - A healthcare provider with graduate-level professional training and clinical experience in psychotherapy, licensed to practice independently, serving as the *lead* monitor. Examples of such professional credentials include the following:

      - Clinical or counseling psychologist (PhD or PsyD)
      - Psychiatrist or other physician (MD or DO)
      - Master of Social Work (MSW)
      - Licensed Clinical Professional Counselor (LCPC)
      - Licensed Marriage and Family Therapist (LMFT)
      - Psychiatric Nurse Practitioner (Psychiatric NP).

[32] 21 CFR 312.42.

336
337 ▪ An *assistant* monitor with a bachelor's degree and at least 1 year of clinical
338 experience in a licensed mental healthcare setting.
339
340 – If the lead monitor is not a physician, availability of a licensed on-call physician able
341 to reach the clinical site within 15 minutes in the event of a medical emergency.
342
343 • The informed consent should clearly describe that subjects may experience changes in
344 perception, cognition, and judgment that persist for many hours, as well as increased
345 vulnerability and suggestibility during the treatment session.
346
347 • Sponsors should plan to characterize the dose-response relationship for both safety and
348 efficacy early in the drug development program.
349
350 • Sponsors should plan to characterize the durability of response for their drug product, the
351 recommended interdose interval for maintenance of effect, and the safety and efficacy of
352 repeat dosing. At a minimum, for the treatment of a chronic illness such as post-traumatic
353 stress disorder or major depressive disorder, sponsors should evaluate the effect of
354 treatment at 12 weeks. However, sponsors should continue to follow subjects in an open-
355 label extension period for a year beyond the Week 12 endpoint to monitor for symptom
356 recurrence or, potentially, the need for repeat dosing.
357
358 • For drugs that have been shown to have functional activity at the 5-HT2B receptor, it is
359 likely that baseline and follow-up echocardiograms to assess valve structure and function
360 and pulmonary artery pressures should be included in the study for drugs that are to be
361 chronically administered. In general, patients with preexisting valvulopathy or pulmonary
362 hypertension should be excluded until the cardiac risk has been characterized.
363 Recommendations for when and how to assess QT interval and blood pressure can be
364 found in the guidance for industry *E14 Clinical Evaluation of QT/QTc Interval*
365 *Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October
366 2005) and the draft guidance for industry *Assessment of Pressor Effects of Drugs*
367 (February 2022).[33]
368
369 • Sponsors should address how adverse events or serious risks are mitigated during the
370 clinical studies and if similar strategies can be implemented post marketing. Sponsors
371 should consider where the drug would be dispensed and administered if approved and
372 whether the healthcare system would be able to prevent nonmedical use, accidental
373 exposure, and overdose for both patients and nonpatients. Sponsors should also consider
374 if gaps exist in the health care system regarding safe use. For the majority of drugs,
375 routine risk mitigation measures, such as providing health care providers with risk
376 information through FDA-approved prescribing information, are sufficient to preserve
377 benefits while minimizing risks. In some cases, however, FDA may consider whether a

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

risk evaluation and mitigation strategy may be necessary to ensure that the benefits of the drug outweigh its risks.[34]

- 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 nonpatients.

[34] See 505-1(a) of the FD&C Act.