A Regulatory Perspective on the Preclinical and Clinical Abuse Potential Evaluation of Psychedelics

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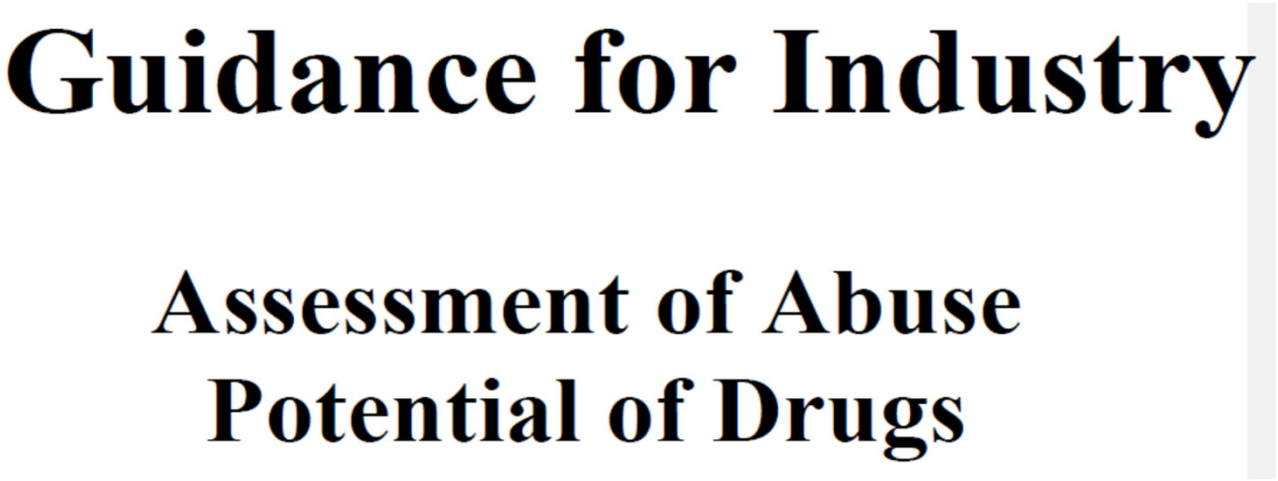
Assessment of Abuse Potential of Psychedelics

Psychedelic Drugs:
Considerations for
Clinical Investigations
Guidance for Industry

This 2023 FDA Guidance describes the principles for how preclinical and clinical research on psychedelics may be conducted – including an assessment of abuse potential.

Assessment of Abuse Potential



This 2017 FDA Guidance describes the principles for how central nervous system (CNS)-active drugs are evaluated for abuse potential.

Assessment of Abuse Potential

- As described in the 2017 Guidance, the assessment of abuse potential includes an evaluation of:
  - Chemistry
  - Pharmacology
  - Behavioral data from animals and humans
  - Adverse events in humans
  - Epidemiological data
- The Guidance recommends that an abuse assessment be conducted at the end of Phase 2, when the final proposed therapeutic dose range has been identified, because abuse-related study doses are based on the therapeutic doses.

Assessment of Abuse Potential

Chemistry

- $5HT_2$ agonist psychedelics:
  - Tryptamines (including ergolines):
    - lysergic acid diethylamide (LSD), psilocybin, dimethyltryptamine (DMT)
  - Phenethylamines:
    - mescaline, 2,5-dimethoxy-4-methylamphetamine (DOM), 2-(4-bromo-2,5-dimethoxyphenyl)ethanamine (2-CB)
- New molecular entities (NMEs) with tryptamine or phenethylamine structures will need to be investigated for psychedelic effects.

Assessment of Abuse Potential

Pharmacology:

- Classic psychedelics and many NMEs with psychedelic effects are $5HT_{2A}$ (and $5HT_{2C}$) agonists.
- These drugs should be assessed for abuse potential as described in the 2017 and 2023 FDA Guidances.

Assessment of Abuse Potential

Pharmacology:

Other mechanisms of action are known to produce hallucinations and altered states of consciousness:

- CB1 agonists: cannabinoids (from *Cannabis sp*.)
- Serotonin transporter inhibitor/releaser: 3,4-methylenedioxymethamphetamine (MDMA)
- *N*-methyl-*D*-aspartate (NMDA) antagonists: ketamine and phencyclidine (PCP)
- Kappa opioid agonist: salvinorin A
- Nonspecific opioid agents: nitrous oxide
- γ-Aminobutyric acid (GABA) agonists: muscimol
- "Z-drug" sedatives: zolpidem, zaleplon, zopiclone, eszopiclone
- Anticholinergics: scopolamine or atropine

Although these are not classic psychedelics, the scientific principles from the 2017 and 2023 Guidances will be applicable.

Assessment of Abuse Potential

Behavioral Studies in Animals:

The 2017 Guidance describes four typical animal behavioral studies that are conducted for evaluating abuse potential:

- Drug discrimination
- Self-administration
- Conditioned place preference
- Physical dependence

Assessment of Abuse Potential

Drug Discrimination (DD):

- In drug discrimination, animals are trained to bar-press on different levers when they receive a training drug (with a specific mechanism of action) and when they receive saline.
- Then the test drug is given at increasing doses to see which lever the animal presses during the session.
- For an abuse potential assessment, the training drug must be a scheduled drug of abuse with a similar mechanism of action to the test drug under development.

Assessment of Abuse Potential

Drug Discrimination (DD):

- When there is full generalization between a test drug and a training drug with known abuse potential, it suggests that the test drug may also have abuse potential.
- During development of $5HT_2$ agonists, the training drug in DD would be a $5HT_2$ agonist. There are decades of research showing full generalization between $5HT_2$ agonists. Subsequent human studies have typically shown that a $5HT_2$ test drug has psychedelic effects.

Assessment of Abuse Potential

Drug Discrimination (DD):

- For classic $5HT_2$ agonist psychedelics (e.g., LSD, psilocybin, mescaline), it will not be necessary to conduct new DD studies since there are already many published DD studies showing full generalization to another $5HT_2$ agonist.
- For novel psychedelics, it will be necessary to conduct new DD studies to determine if they generalize to known psychedelics or other drugs of abuse, depending on their mechanism of action.

Assessment of Abuse Potential

Self-Administration (SA):

- In self-administration, animals are trained to bar-press to receive a small intravenous dose of a known drug of abuse as the training drug.
- This produces repeated bar-pressing for more drug, showing that the training drug has rewarding properties that are reinforcing.
- For regulatory SA studies, the training drug must be a drug scheduled under the Controlled Substances Act (CSA).
- Then the test drug is introduced and if it produces self-administration, it shows that it also has rewarding effects that are reinforcing.

Assessment of Abuse Potential

Self-Administration (SA):

- Most known drugs of abuse are self-administered by animals (e.g., opioids, benzodiazepines, stimulants, etc.). This is considered predictive of human self-administration for rewarding purposes.
- However, decades of research have shown that classic $5HT_2$ psychedelics are not typically self-administered by animals, despite epidemiological data showing that humans do self-administer them.

Assessment of Abuse Potential

Self-Administration (SA):

- Thus, it will not be necessary to conduct new SA studies with classic $5HT_2$ agonist psychedelics.
- For novel $5HT_2$ agonist psychedelics, it is also unlikely that SA studies would be required.
- However, for psychedelics with novel mechanism(s) of action, the need for SA studies would depend on whether those other mechanisms were previously associated with animal SA.

Assessment of Abuse Potential

Conditioned Place Preference (CPP):

- In CPP, animals receive a test drug on one side of a cage and saline on the other side – with each side having distinct qualities and a barrier in-between.
- If the test drug has rewarding properties, the animal will be more likely to be on the side where it received the test drug, when the barrier between the two sides is removed.
- Thus, CPP is a less technologically complex method than SA for evaluating the rewarding properties of a drug.

Assessment of Abuse Potential

Conditioned Place Preference (CPP):

- There are no published studies in the scientific literature reporting on CPP with classic psychedelics (e.g., LSD and psilocybin). This is likely because of the inability to produce SA with these drugs.
- Thus, for psychedelics, classic or novel, the principles described for when SA will be necessary will also apply to CPP.

Assessment of Abuse Potential

Physical Dependence:

- Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.
- Typically, drugs for the treatment of psychiatric disorders are administered on a daily basis. This repeated use may produce a withdrawal syndrome upon drug discontinuation, indicating the development of physical dependence.

Assessment of Abuse Potential

Physical Dependence:

- However, the psychedelic model for treatment of psychiatric disorders typically involves drug administration only once or on several occasions separated by days or weeks. This dosing regimen is not conducive to the physiological development of physical dependence.
- Thus, it is unlikely that a physical dependence assessment would be required in animals (or humans) for psychedelics that are proposed for acute or intermittent use. If a psychedelic were proposed for daily use, a physical dependence assessment will likely be recommended.

Assessment of Abuse Potential

Abuse Evaluations in Humans:

The 2017 Guidance describes three methods for evaluating abuse potential in humans:

- Evaluation of abuse-related adverse events
- Human abuse potential studies
- Epidemiological data

Assessment of Abuse Potential

Evaluation of Abuse-Related Adverse Events (AEs)

- During clinical studies in Phase 1 (with healthy individuals) and in Phases 2/3 (with patients), the evaluation of abuse-related AEs provides the first evidence in humans if there are safety signals that may need further evaluation.
- The 2017 Guidance delineates abuse-related AEs (based on Medical Dictionary for Regulatory Activities; MedDRA) that are monitored during clinical studies with CNS-active drugs.

Assessment of Abuse Potential

Evaluation of Abuse-Related Adverse Events (AEs)

Euphoria-related terms

- Euphoric mood; Elevated mood*;* Feeling/thinking abnormal; Hallucination

Terms indicative of impaired attention, cognition, and mood

- Somnolence; Mood disorders and disturbances

Dissociative/psychotic terms

- Psychosis; Aggression; Confusion; Disorientation

Related terms not captured elsewhere

- Drug tolerance; Substance-related disorders

Assessment of Abuse Potential

Evaluation of Abuse-Related Adverse Events (AEs)

- It is important to note that all effects that occur during a clinical study are monitored as “adverse events,” even if they are responsible for the therapeutic effects or are expected to occur based on our knowledge of the drug class (e.g., the AE of sedation for a drug to treat insomnia).
- Thus, "hallucinations" and "thinking abnormally" are monitored as AEs for psychedelics, even though they are expected as clinical responses and are hypothesized by some to be part of the therapeutic effects.

Assessment of Abuse Potential

Evaluation of Abuse-Related Adverse Events (AEs)

- For psychedelics with multiple mechanisms of action, there may be additional AEs that are observed, which provide information about the full range of the drug's effects.
- However, in the absence of a euphoria signal or hallucinations, the drug is unlikely to have abuse potential.

Assessment of Abuse Potential

Human Abuse Potential (HAP) Study:

- For most CNS-active drugs that show signals of animal or human abuse potential, a HAP study will typically be required.
- HAP studies use subjects who have experience with a class of drugs that is similar to that of the test drug.
- HAP studies evaluate the highest proposed therapeutic dose of the test drug, plus doses that are 2-3X higher (if this can be done safely), in comparison to placebo and a comparator with similar behavioral effects (and similar mechanism of action, if possible) that is scheduled under the CSA.

Assessment of Abuse Potential

Human Abuse Potential (HAP) Study:

- Conceptually, there are reasons why a HAP study with psychedelics may not be necessary.
- These reasons are based on scientific principles and on safety considerations for the subject.
- Thus, the need for a HAP study will be determined by an evaluation of these concepts for each individual psychedelic, based on its mechanism of action, proposed doses, patient population, and known adverse event profile.

Assessment of Abuse Potential

Human Abuse Potential (HAP) Study:

Scientific Principles Underlying HAP Studies:

- HAP studies provide early prospective data on whether an NME produces rewarding effects that are suggestive of abuse potential.
- HAP studies should test the highest proposed therapeutic dose plus doses that are 2-3X higher.
- The positive control will be an FDA-approved drug in Schedule II, III, IV, or V of the CSA with similar mechanism or behavioral effects as the test drug,.
- Subjects participate in a Qualification Phase (1-2 doses of each positive control vs. placebo) and a Test Phase (1-2 doses of each positive control, 1-3 doses of test drug, plus placebo).
- Session monitors must have appropriate qualifications, based on the 2023 FDA Guidance.

Assessment of Abuse Potential: HAP Study

Scientific Principle: HAP studies provide early prospective data on whether an NME produces rewarding effects that are suggestive of abuse potential

- However, we already know that classic psychedelics (e.g., LSD, psilocybin, MDMA) are used recreationally, based on epidemiological data over the past 70 years.
- This suggests that the scientific rationale for a HAP study with classic psychedelics has already been fulfilled by epidemiological data.

Assessment of Abuse Potential: HAP Study

Scientific Principle: HAP studies should test the highest proposed therapeutic dose plus doses that are 2-3X higher

- Generally, proposed therapeutic doses do not produce pronounced signals of euphoria or other rewarding effects.
- Since recreational drug use typically occurs at supratherapeutic doses, this is why higher doses are tested in HAP studies.
- If a drug has abuse potential, supratherapeutic doses will likely produce rewarding responses.

Assessment of Abuse Potential: HAP Study

Scientific Principle: HAP studies should test the highest proposed therapeutic dose plus doses that are 2-3X higher (continued)

- But in clinical studies with MDMA and psilocybin that have been published to date, the therapeutic doses are within the range of doses that are used recreationally.
- Thus, the lower, therapeutic dose in a HAP study would already be known to produce rewarding effects that support recreational use, based on epidemiological data.
- Therefore, there is little scientific justification for testing the therapeutic dose of a psychedelic in a HAP study.

Assessment of Abuse Potential: HAP Study

Scientific Principle: HAP studies should test the highest proposed therapeutic dose plus doses that are 2-3X higher (continued)

- The use of psychedelic doses in a HAP study that are 2-3X higher than the therapeutic dose raises important safety and ethical questions.
- **Physiological** responses are likely to increase if psychedelic doses were increased 2-3X, so there must be a viable scientific rationale to justify such high doses.

Assessment of Abuse Potential: HAP Study

Scientific Principle: HAP studies should test the highest proposed therapeutic dose plus doses that are 2-3X higher (continued)

- However, we already know from epidemiological data that **therapeutic** doses of psychedelics have abuse potential, which fulfills the purpose of a HAP study.
- Thus, it is difficult to scientifically justify administering psychedelics at **supratherapeutic** doses, when that means exposing subjects to the risk of increased degrees of such AEs as hypertension or gastrointestinal distress.

Assessment of Abuse Potential: HAP Study

Scientific Principle: HAP studies should test the highest proposed therapeutic dose plus doses that are 2-3X higher (continued)

- The **psychological** responses to psychedelics are profound enough at therapeutic doses that subjects typically receive pre- and post-session psychological care to reduce the likelihood of unpleasant responses.
- Additionally, the doses for therapeutic investigation were specifically selected because the psychological responses were manageable under clinical care.

Assessment of Abuse Potential: HAP Study

Scientific Principle: HAP studies should test the highest proposed therapeutic dose plus doses that are 2-3X higher (continued)

- The purpose of a HAP study is to predict abuse potential. Epidemiological data have already shown that psychedelics are recreationally used.
- Therefore, it is especially difficult to scientifically justify administering psychedelics at **supratherapeutic** doses, when that means exposing subjects to the risk of massively increased **psychological** responses that may prove to be much more difficult to clinically manage than the therapeutic dose.

Assessment of Abuse Potential: HAP Study

Scientific Principle: HAP studies should test the highest proposed therapeutic dose plus doses that are 2-3X higher (continued)

- Administering very high doses of psychedelics that place subjects into an intense psychedelic state without scientific justification or therapeutic intent raises serious ethical issues and clinical management issues.
- FDA has previously prevented clinical efficacy studies with psychedelics to proceed when the proposed doses were very high and not likely to be well-tolerated psychologically.

Assessment of Abuse Potential: HAP Study

Scientific Principle: HAP studies should test the highest proposed therapeutic dose plus doses that are 2-3X higher (continued)

- For NME psychedelics without a history of recreational use, the need for a HAP study will depend on whether the proposed therapeutic doses produce psychedelic responses in clinical studies.
- If they do, this indicates that the drug has abuse potential and that a HAP study may not be needed.

Assessment of Abuse Potential: HAP Study

Scientific Principle: HAP studies should test the highest proposed therapeutic dose plus doses that are 2-3X higher (continued)

- For NME psychedelics that do not produce psychedelic responses at therapeutic doses, a HAP study may be considered, depending on physiological and psychological safety considerations.
- This would also apply to "non-psychedelic psychedelic" drugs that are structurally similar to psychedelics but are alleged to not produce psychedelic effects at therapeutic doses.

Assessment of Abuse Potential: HAP Study

Scientific Principle: The positive control will be an FDA-approved drug in Schedule II, III, IV, or V of the CSA with similar mechanism or behavioral effects as the test drug

- There are currently no FDA-approved $5HT_2$ agonists that can serve as a positive control for psychedelic studies (since lorcaserin is no longer marketed and other $5HT_2$ agonists are still under development).
- The HAP study for lorcaserin utilized ketamine and zolpidem as positive control drugs, but these are not $5HT_2$ agonists and were not ideal positive controls. Thus, selection of a positive control for psychedelic studies is difficult since Schedule I psychedelics are not suitable to serve as a positive control.

Assessment of Abuse Potential: HAP Study

Scientific Principle: Subjects participate in a Qualification Phase (1-2 doses of each positive control vs. placebo) and a Test Phase (1-2 doses of each positive control, 1-3 doses of test drug, plus placebo)

- Given the profound psychological responses to a psychedelic (or similar positive control), this raises questions about whether it is ethical to place subjects into this state up to 11 times, especially when a HAP study may be difficult to justify scientifically.
- This also raises questions about what sort of post-session integration care would be required for such frequent psychedelic exposure, since the frequency is so different than the typically proposed therapeutic use of only 1-3 exposures.

Assessment of Abuse Potential: HAP Study

Scientific Principle: Session monitors must have appropriate qualifications, based on the 2023 FDA Guidance

- Typically, HAP studies are conducted by investigators with special experience in running HAP studies.
- However, for psychedelic studies, FDA has required that two people with specific qualifications be in the session room during the entire 8- to 12-hour psychedelic session.
- These qualifications would be required for monitors of HAP studies with psychedelics.

Assessment of Abuse Potential: HAP Study

Scientific Principle: Session monitors must have appropriate qualifications, based on the 2023 FDA Guidance

- The **Lead Monitor** will be a healthcare provider with graduate-level professional training and clinical experience in psychotherapy, licensed to practice independently.
- Examples of credentials include:
  - 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)

Assessment of Abuse Potential: HAP Study

Scientific Principle: Session monitors must have appropriate qualifications, based on the 2023 FDA Guidance

- If the lead monitor is not a physician, there must be availability of a licensed on-call physician who is able to reach the clinical site within 15 minutes in the event of a medical emergency.
- **Assistant Monitor** credentials include a bachelor's degree and at least 1 year of clinical experience in a licensed mental healthcare setting.

Assessment of Abuse Potential

Alternatives to a HAP Study

- In lieu of a HAP study, validated scales such as the Mystical Experience Questionnaire (MEQ-30), the Hallucinogen Rating Scale, and the 5-Dimension Altered States of Consciousness Questionnaire may be used to monitor the psychedelic experience of patients in clinical studies, as well as changes in positive subjective responses (such as drug liking or euphoria).

- These measures will provide information about whether there is a dose-response correlation, as well as the extent to which the responses to the therapeutic dose overlap with acute rewarding effects in patients.

Assessment of Abuse Potential

Epidemiological Data:

- For most NMEs, there are no epidemiological data because the drug has not been previously FDA-approved and has not been available on the street.
- However, for classic psychedelics, there are seven decades of epidemiological data showing that these drugs have been extensively used recreationally.
- These epidemiological data will help inform an abuse potential assessment of the classic psychedelics.

Assessment of Abuse Potential

Epidemiological Data:

- There may be epidemiological data for recreational use of novel psychedelics that are under development.
- However, the extent of the data may be limited and verification of the identity of the drug may not be available.
- Where there are no epidemiological data for a novel psychedelic, available epidemiological data on drugs with a similar mechanism or effects may be used to suggest abuse potential if the drug were diverted from medical use.

Impact of FDA Abuse Potential Assessment

- If an NDA for a psychedelic is submitted in the future, the Controlled Substance Staff (CSS) evaluates all the abuse-related data to determine whether that the drug has abuse potential. This determination will inform two things:
  - **Drug Label**: Section 9 (Drug Abuse and Dependence)
  - **Scheduling under the CSA**: An HHS recommendation for scheduling placement under the CSA, based on a scientific and medical evaluation of abuse-related data, with final placement by DEA.

CONCLUSIONS

- Psychedelics are assessed for abuse potential following the principles described in the 2017 and 2023 FDA Guidances.
- However, there are unique aspects of psychedelics that may allow for modifications of the kinds of studies that are required for a full abuse potential assessment.
- Discussions with CSS during drug development will clarify which abuse-related animal and human data will be necessary prior to submission of an NDA.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