# Navigating the Unchartered Territory of Assessing Psychedelics in Human Abuse Potential Studies

**Setnik B,[1] Martynowicz J,[2] Coulson A,[3] Diaz JC,[4] Inamdar A,[5] Malhotra S,[6] Milovan D,[1] Price C,[7] Roberts C,[8] Tsai J,[9] Yazar-Klosinski B[10]**

**[1]Altasciences, QC, Canada; [2]Neokee Pharma Consulting LLC, [3]NTH Consulting Inc, [4]GeoSera, [5]Cybin, [6]Neuro-Behavioral Clinical Research Inc, [7]UCLA, West LA VA Medical Center, [8]Beckley Psytech Ltd, [9]Independent, [10]Lykos Therapeutics**

## ABSTRACT

Introduction: Psychedelics' unique pharmacological properties necessitate adaptations in Human Abuse Potential (HAP) study methodology to assess their pleasurable and reinforcing effects. To date, no formal HAP study has been conducted for FDA drug approval purposes. These studies, typically double-blind, randomized, crossover single-dose, placebo- and active-drug controlled, are designed to evaluate abuse potential in non-dependent recreational drug users. They assess subjective effects using various endpoints, including the maximum Drug Liking score on a bipolar visual analog scale (VAS), with secondary measures such as overall drug liking, desire to take the drug again, and adverse events (AEs), including abuse-related AEs.

Psychedelics present challenges in HAP studies due to their mixed positive and negative effects, which can increase endpoint variability, compromise validity, and complicate data interpretation. Functional unblinding, resulting from the perceptual distortions often induced by psychedelics, further complicates these studies. Consequently, HAP methods must be adapted for psychedelic substances.

Methods: A working group of clinical trial experts reviewed the 2017 FDA guidance on HAP studies and explored its application to psychedelics. Meetings focused on identifying limitations in current methods and proposing revisions to study endpoints, dose selection, identification of active controls, blinding, and safety oversight.

Results: The working group proposed several adaptations to better evaluate novel psychedelics in HAP studies. Dose selection should prioritize safety, with an emphasis on avoiding supratherapeutic levels if their inclusion is deemed unnecessary or unsafe. Including a minimally effective dose in the qualification phase may reduce expectancy effects and functional unblinding. During treatment, a range of therapeutic doses, from minimal to maximum, could further mitigate these issues and help establish dose-response relationships. Until other psychedelics are FDA-approved, positive controls may be limited to ketamine or dextromethorphan. While the bipolar VAS for Drug Liking has not been used with psychedelics, it may also have limited predictive validity; instead the Take Drug Again VAS may be a suitable primary endpoint substitute. Statistical adaptations may be needed to ensure validity, including considering a lower margin for primary endpoint differences between the positive control and placebo. Monitoring participants should focus on safety, given the healthy volunteer population without neuropsychiatric conditions, to minimize bias and promote consistency.

Conclusions: HAP studies for psychedelics require methodological modifications to address their unique pharmacological properties. Study endpoints, analysis, and data interpretation must account for the variability in subjective responses. Dose selection, positive controls, blinding, and monitoring interventions will also need to be carefully tailored to ensure valid results.

## INTRODUCTION

The FDA requires HAP studies to assess the reinforcing properties of centrally active drugs in healthy, non-dependent recreational drug users. While these studies are well-established for conventional drugs of abuse, their application to psychedelics is underdeveloped and no psychedelic has yet been evaluated in a formal HAP study. The FDA Draft Guidance for Psychedelic Drugs (June 2023) specifies that:

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

Psychedelic compounds, such as psilocybin and LSD, possess unique pharmacological profiles that complicate traditional evaluations of abuse potential. Unlike typical CNS stimulants or depressants, psychedelics induce a range of perceptual, emotional, and cognitive effects—both positive and negative—that vary significantly across individuals. Functional unblinding (where drug effects reveal treatment identity), lack of appropriate controls, and endpoint variability variables are challenging the face validity of standard Human Abuse Potential (HAP) study methodologies (**Figure 1**).

To date, there have been no published HAP studies conducted for psychedelics that follow the FDA Guidance on abuse potential evaluation to support NDA submissions. The abuse potential of psychedelics have been evaluated in academic studies that utilize similar, but not exact methodological approaches required by the FDA.

## METHODOLOGY

The International Society of CNS Clinical Trials and Methodology (ISCTM) established a multidisciplinary working group to review the FDA's 2017 guidance on the assessment of abuse potential and examine its applicability to psychedelic drugs. Discussions centered on modifications to standard HAP designs across several domains: qualification procedures, dose selection, endpoint selection, control conditions, blinding integrity, statistical analysis, and facilitation.

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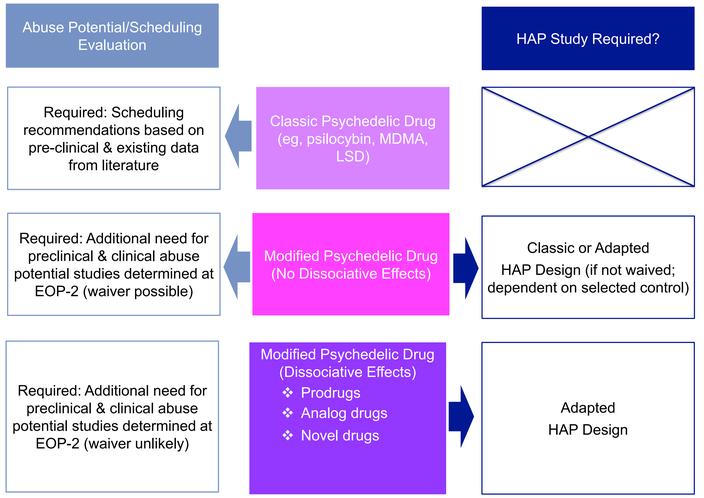
### *Anatomy of a Traditional HAP Study*

- HAP studies are typically randomized, double-blind, placebo- and active-controlled crossover trials. Participants complete a qualification phase, during which their ability to distinguish a known drug of abuse (positive control) from placebo is assessed based on subjective responses (eg, peak Drug Liking score ≥65 and ≥15 points above placebo).
- Upon qualification, participants enter the treatment phase, receiving single doses of the investigational drug (therapeutic and supratherapeutic range), placebo, and positive control under double-blind conditions.
- The primary endpoint is the maximum Drug Liking score (bipolar VAS), while secondary outcomes include various endpoints such as Take Drug Again, Overall Drug Liking, and other measures of drug effects (eg, High, Good Effects, Bad Effects, Any Drug Effects), alongside safety and tolerability assessments (**Figure 2**).

**Figure 1.** Abuse Potential Requirements for Psychedelics




### *Psychedelics HAP Study Adaptations*

#### Dose Selection

- During treatment, single doses in the low, therapeutic, and supratherapeutic (where feasible) range are typically recommended to establish dose-response relationships.
- Investigators should avoid supratherapeutic doses, if unnecessary or unsafe.
- Consider low doses to establish dose-response relationship and mitigate functional unblinding.

#### Control Conditions and Blinding

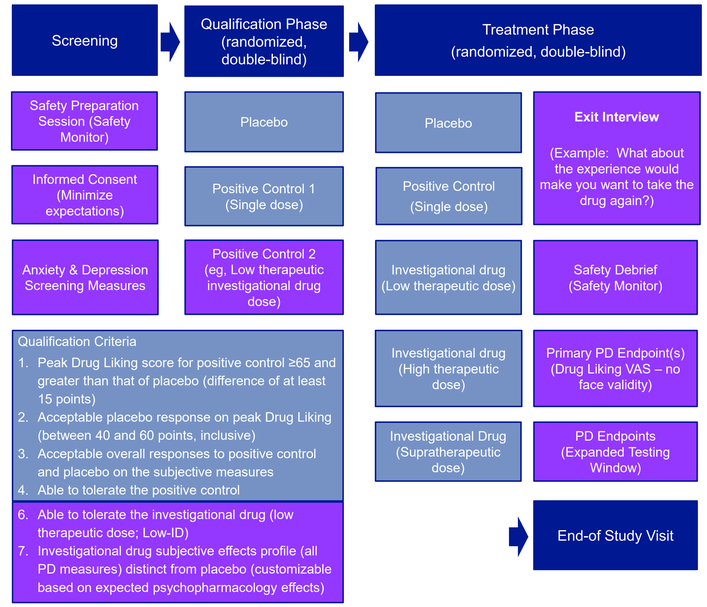
- Ketamine and dextromethorphan may serve as viable positive controls due to their approval status and dissociative effects. As additional psychedelics gain regulatory approval, these may be incorporated as comparators.
- Pseudo-placebos (a minimally effective dose of the study drug or another active drug with dissociative effects may be included to address the potential for functional unblinding).
- Multiple-dummy techniques and route-matched administration strategies may be needed to preserve blinding.

#### Expectancy Management

- Standardize all environmental (ie, setting) and interpersonal conditions (ie, clinical staff and study monitors)
- Monitoring must be manualized, neutral, and non-directive, to avoid influencing subjective reports.
- Monitoring must be performed by professionals trained per FDA competencies (ie, licensed clinicians for lead monitors and clinically experienced assistants).
- Study monitors must remain focused on safety oversight, not therapeutic guidance.
- Expectancy assessment tools post drug administration session (Qualification and Treatment phases) ask participants to report what drug they believe they received.

**Figure 2** provides a schema of study design adaptations that may be considered when planning to evaluate the abuse potential of psychedelics.

**Figure 2.** Classic *vs.* Modified HAP Study Design




#### Study Endpoints & Analyses

- Negative drug effects may impact Drug Liking scores rendering the traditional Drug Liking VAS less predictive.
- The Take Drug Again VAS may posses improved face validity and prove to be a more meaningful primary endpoint.
- Expanded testing windows for all traditional HAP endpoints should be considered to capture the delayed or evolving effects of psychedelics.
- Adaptations for positive control *vs.* placebo must be considered to avoid implementing invalid sensitivity analyses.
- Modified completer population requirements must be adapted to exclude true outliers (eg, removal of subjects reporting "drug dislike" may not be appropriate for psychedelics).

#### Set and Setting

- Consider impact of environment on subjective drug experience.
- Controlled, consistent environment at each dosing.

## DISCUSSION

Current HAP methods, though robust for many CNS-active drugs, are not fully transferable to psychedelic substances. Key concerns include the reliability of subjective endpoints, the high potential for functional unblinding, and the complex pharmacodynamics of psychedelics. Incorporating lower doses, reassessing endpoint validity, and prioritizing participant safety and neutrality of conditions are critical for generating interpretable and regulatory-relevant findings.

## CONCLUSIONS

- Psychedelics require tailored HAP methodologies that address their unique pharmacological and experiential features. By refining study designs — particularly dose selection, blinding strategies, control drug choices, and endpoint definitions — researchers can better assess the true abuse potential of these substances.
- Ongoing collaboration between academia, industry, and regulators is essential to develop rigorous, ethical, and scientifically sound frameworks.

**Disclosures:** The viewpoints expressed are those of the authors and not their respective employers. The authors report no conflicts of interest for this work.

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