REAGAN-UDALL FOUNDATION FOR THE FDA

Advancing Psychedelic Clinical Study Design

MEETING SUMMARY
JUNE 2024

TABLE OF CONTENTS

This activity is one part of a multi-part Foundation project related to substance use disorder. The multi-part project is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of an overall award of $1,720,109 of federal funds (100% of the project). The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA, HHS, or the U.S. Government. For more information, please visit FDA.gov.

1. Introduction

On January 31 and February 1, 2024, the Reagan-Udall Foundation for the FDA, in collaboration with the FDA, hosted a virtual public workshop bringing together researchers, academics, industry, regulators, and other key stakeholders to discuss scientific issues that arise while working with psychedelics in clinical trials and drug development. In June 2023, the FDA issued its first draft guidance for industry, *Psychedelic Drugs: Considerations for Clinical Investigations*,[1] to provide general considerations to sponsors developing psychedelic drugs for the treatment of medical conditions (e.g., psychiatric disorders, substance use disorders). While the guidance highlights some of the challenges in designing clinical trials with psychedelics capable of yielding interpretable results, many questions remain about the most appropriate way to address these challenges. This workshop explored empirical approaches to address key issues in psychedelic drug development and research. Meeting goals included:

1. Understanding the experiences of scientists working with psychedelics in FDA-authorized clinical studies and drug development
2. Exploring considerations for psychedelic clinical trial designs
3. Exploring perspectives and current research on set and settings in psychedelic clinical trials
4. Providing an overview of the June 2023 draft FDA guidance for industry: *Psychedelic Drugs: Considerations for Clinical Investigations*

This document summarizes the presentations and panel discussions from the meeting, exploring the scientific issues that arise while working with psychedelics in clinical trials and the evolving landscape of psychedelic research. This summary report does not represent the official ideas or policies of the FDA.

BACKGROUND

The term *psychedelic*, derived from Greek *psykhē* (mind) plus *dēloun* (make visible, reveal), is defined as "producing expanded consciousness through heightened awareness and feeling".[2] Psychedelic drugs can cause intense perceptual disturbances and alterations in consciousness.[3]

Psychedelics have been described as "drugs of wonder," giving an individual access to profound mystical experiences and sensations of wonder and awe. However, these drugs are not "wonder drugs"—panaceas that fix everything. Scientific findings are not generalizable across all psychedelic drugs or across disorders. It is important that scientific information for each drug be evaluated individually in the context of the drug, dose, and proposed therapeutic use.[4]

1 U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Psychedelic Drugs: Considerations for Clinical Investigations, Guidance for Industry, Draft Guidance. June 26, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/psychedelic-drugs-considerations-clinical-investigations.

2 Online Etymology Dictionary. Accessed April 1, 2024. https://www.etymonline.com/word/psychedelic

3 U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Psychedelic Drugs: Considerations for Clinical Investigations, Guidance for Industry, Draft Guidance. June 26, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/psychedelic-drugs-considerations-clinical-investigations

4 Yaden DB, Griffiths RR. The Subjective Effects of Psychedelics Are Necessary for Their Enduring Therapeutic Effects. ACS Pharmacol Transl Sci. 2020 Dec 10;4(2):568–572. doi: 10.1021/acsptsci.0c00194.

Currently, there is no FDA-approved psychedelic drug,[5] and FDA has not made conclusive determinations about the safety or efficacy of any psychedelic drug. Drugs discussed during the meeting include the classic psychedelics such as psilocybin and LSD,[6] and MDMA[7] (sometimes considered an "entactogen" or "empathogen")[8] which will collectively be referred to as "psychedelics" within this report. Also, in this report, each section will begin with an excerpt from the FDA draft guidance or other federal standard, followed by highlights from the corresponding workshop discussions and key takeaways pertinent to that topic.

5 Psychedelics (psilocybin, LSD, and MDMA) are Schedule I under the Controlled Substances Act

6 Lysergic acid diethylamide

7 3,4-Methylenedioxymethamphetamine

8 A novel class of psychoactive agents. An entactogen produces experiences of empathy or sympathy rather than hallucinogenic effects.

2. FDA Guidance and Regulatory Considerations

During the workshop, Dr. Tiffany Farchione from the Division of Psychiatry within CDER provided an overview of the FDA's draft guidance for industry and reviewed the FDA's regulatory authority. Aspects of these presentations are provided below.

A) DRAFT GUIDANCE FOR INDUSTRY: *PSYCHEDELIC DRUGS: CONSIDERATIONS FOR CLINICAL INVESTIGATIONS (2023)*

In June 2023, the FDA published a draft guidance for sponsors developing psychedelic drugs for the treatment of medical conditions. Guidance documents represent the FDA's current thinking on the topic and do not establish legally enforceable responsibilities.[9] It is noteworthy that the FDA does not regulate the practice of medicine, including psychotherapy. The guidance describes considerations relevant to every stage of research, from basic science investigations through clinical trials, and provides strategies for the areas listed in Table 1. The guidance can be found here: https://www.fda.gov/media/169694/download

Table 1: Draft Guidance Content

CONTENT AREA	REFERENCES & GUIDANCE
Chemistry, Manufacturing, and Controls	Current good manufacturing practice (cGMP) compliance
Nonclinical studies	ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010)[10]
Clinical pharmacology	In vitro and in vivo pharmacokinetics and pharmacodynamics of psychedelic drugs Pharmacokinetic and Pharmacodynamic Interactions • Drug-drug interactions • Drug-disease interactions Dose-response relationship for safety and efficacy
Abuse potential assessment	Component of the safety evaluation FDA Guidance for the *Assessment of Abuse Potential of Drugs* (2017)[11]

9 Office of Regulatory Affairs. Guidances. Food and Drug Administration. Accessed April 1, 2024. https://www.fda.gov/industry/fda-basics-industry/guidances

10 Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. U.S. Food and Drug Administration. Published January 2010. Accessed March 28, 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m3r2-nonclinical-safety-studies-conduct-human-clinical-trials-and-marketing-authorization

11 Center for Drug Evaluation and Research. Assessment of Abuse Potential of Drugs. U.S. Food and Drug Administration. Published January 2017. Accessed March 28, 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessment-abuse-potential-drugs

Clinical considerations	Adequate and well-controlled (AWC) clinical studies as defined by the Code of Federal Regulations (21 CFR 314.126) and challenges to designing AWC studies with psychedelics. • Study design that permits a valid comparison with a control • Study design that minimizes bias FDA Guidance for *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)[12]

B) FDA PRESCRIPTION DRUG REGULATORY AUTHORITY

The FDA regulates product labeling to ensure that it contains the essential scientific information needed for the safe and effective use of the drug (21 CFR 201.56). FDA does not regulate the practice of medicine, including psychotherapy; however, labeling regulations allow for specification that a drug should be used only in conjunction with another mode of therapy, as in the examples below.

> 21 CFR 201.57(c)(2)(i)(A): If the drug is used for an **indication only in conjunction with a primary mode of therapy** (e.g., diet, surgery, behavior changes, or some other drug), **a statement that the drug is indicated as an adjunct to that mode of therapy**.[13]

Table 2. Psychotherapy-Relevant Labeling Precedents[14]

DRUG AND INDICATION	LABEL SECTION	TEXT
Naltrexone extended-release injectable suspension for alcohol and opioid dependence	Indications and Usage	"Treatment … **should be a part of a comprehensive management program that includes psychosocial support**."
Bupropion hydrochloride extended-release tablets for smoking cessation	Dosage and Administration	"It is important that patients continue to receive **counseling and support throughout treatment … and for a period of time thereafter**."
Buprenorphine sublingual tablets for opioid dependence	Clinical Studies	"All trials used **buprenorphine in conjunction with psychosocial counseling as part of a comprehensive addiction treatment program**. There were no clinical studies conducted to assess the efficacy of buprenorphine as the only component of treatment."

12 Center for Biologics Evaluation and Research, Center for Drug Evaluation and Research. Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products. Guidance for Industry. U.S. Food and Drug Administration. Published December 2019. Accessed March 28, 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products.

13 Ibid.

14 Ibid.

3. Psychedelic Clinical Study Design

The next sections provide summaries of topics covered during the meeting. The content within the callout boxes at the start of each section is sourced from the FDA guidance. Information shared during the public meeting discussions does not necessarily reflect the official views and policies of the FDA.

EXCERPT FROM FDA GUIDANCE

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

In an AWC study, adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data.

Researchers report unique challenges when studying psychedelic drugs. Challenges with placebo and nocebo[15] effects and expectancy bias are inherent in central nervous system (CNS) clinical research. These effects are particularly concerning in the study of psychedelics given the significant risk for functional unblinding.[16] Factors that may complicate efficacy assessment and data interpretation when studying psychedelics are listed in Table 3.

Table 3. Challenges in Studying Psychedelics

- Blinding methods
- Pre-, within-, and post-trial expectations (e.g., expectation bias)
- Study context (set and setting)
- Outcome definitions (efficacy, adverse effects)
- Factors that may influence the dynamic of the psychedelic experience and outcome (psychotherapy, concurrent treatment)
- Appropriate comparator in controlled studies
- Determining an appropriate length of follow-up
- Variable access/diversity in study populations

Presenters and panelists discussed the tension between balancing the unique perceptual effects of psychedelics and psychedelic exceptionalism in designing and conducting clinical trials.[17]

15 When a trial participant's expectation of a negative effect from a treatment causes the treatment to have a more negative effect than otherwise.

16 Functional unblinding occurs when someone takes a psychedelic and they are certain they have received active drug based on its effects or are certain that they have received placebo because they haven't experienced physiologic or perceptual effects.

17 Barrow R. Dosing; January 31, 2024. Hartogsohn I, Yaden. Set and Setting; February 1, 2024. Marks M. Considerations for Potential Psychedelic Use in the Real World; February 1, 2024. https://reaganudall.org/news-and-events/events/advancing-psychedelic-clinical-study-design

> So, there is a constant tension and sort of balance that we have to pursue between the uniqueness, the seemingly uniqueness of the perceptual effects of these drugs and how we integrate that into standard research paradigms, how we ultimately come to valid internal and externally valid conclusions about the safety and effectiveness of these product …" — Mr. Robert Barrow

The properties unique to psychedelics warrant close attention when thinking about psychedelic study design. How to account for the specific nature of perceptual changes and associated potential risks, as well as the potential for clinical activity that extends far beyond acute drug exposure, will depend on the drug, dose(s), and condition being studied. Studies illustrating how researchers addressed these issues were presented during the workshop; detailed descriptions of these studies can be found in sessions 2 and 3 here: https://reaganudall.org/news-and-events/events/advancing-psychedelic-clinical-study-design.

While functional unblinding occurs to varying degrees in studies for many types of CNS active drugs, the magnitude of noticeable difference between a psychedelic and a comparator is more profound than for non-psychedelics products. In response to the question of whether telltale signs during clinical trials with other classes of psychiatric drugs are less problematic than more florid signs of psychedelic drugs in terms of unblinding, Dr. Michael Davis from Usona Institute stated the following:

> And I do think this is an issue with many psychiatric drugs or even other classes of drugs that the adverse events or appreciable psychoactive effects can lead to some degree of functional unblinding. I think psychedelics, it's particularly because of the intense acute psychoactive experiences, I think it's a very salient issue…"

In response to the challenges encountered when studying psychedelics, a potential solution may not require study design changes, but rather developing a psychedelic research program that incorporates a combination of different designs in order to adequately answer research questions required for regulatory approval.

ADDITIONAL CONSIDERATIONS

- How unusual are psychedelics, beyond qualitative perceptual effects?
- Do these effects demand differently designed trials or a change in fundamental principles of clinical trials?[18]

KEY POINTS: STUDY DESIGN CONSIDERATIONS

- Psychedelic drug characteristics (e.g., perceptual changes) increase the risk for functional unblinding in a manner distinct from other CNS active drugs
- Placebo and nocebo effects need to be assessed and may affect study outcomes

18 Barrow R. Advancing Psychedelic Clinical Study Design; January 31, 2024. https://reaganudall.org/news-and-events/events/advancing-psychedelic-clinical-study-design

A) SELECTING A VALID COMPARISON

EXCERPT FROM FDA GUIDANCE

An AWC study uses a design that permits a valid comparison with a control to provide a quantitative assessment of a drug's effect. 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 … may be considered as well.

A valid comparison requires the use of a control against which the psychedelic drug is compared. In psychedelic studies, this may include the use of an inactive (inert) placebo or an active comparator. A traditional placebo has no known efficacy or adverse effects, whereas an active comparator mimics some aspects of the psychedelic being studied (e.g., physiologic sensations).

Comparisons may also be made to a lower dose of the psychedelic which may cause some physiologic but subtherapeutic effects and may provide additional valuable dose-response information. The ideal comparator will depend on the psychedelic being studied, known dose-response effects, and the context of the therapeutic intervention.

ADDITIONAL CONSIDERATIONS

- How do active comparator controls impact blinding, study validity, and interpretability?
- Do blinding and study validity need to be linked separately from interpretability?

KEY POINTS: USING A VALID COMPARISON

- Historical data may guide the selection of the best comparator
- An inert placebo may suffice for safety studies, but may be problematic for efficacy studies

B) BLINDING AND EXPECTANCY

From the International Conference on Harmonisation (ICH), "Blinding or masking is intended to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical trial arising from the influence which the knowledge of treatment may have on the recruitment and allocation of subjects, their subsequent care, the attitudes of subjects to the treatments, the assessment of end-points, the handling of withdrawals, the exclusion of data from analysis, and so on. The essential aim is to prevent identification of the treatments until all such opportunities for bias have passed."*

AWC studies employ a valid comparison, minimize bias, and utilize well-defined and reliable response assessments. In many cases, the gold standard for study design meeting AWC is the randomized, double-blind, placebo-controlled trial. The FDA draft guidance "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products" (December 2019) illuminates the impact of unblinding on study results.^

"Poor execution can render a trial of any design to be not adequate or not well-controlled and, therefore, unable to provide substantial evidence of effectiveness. [An example of this includes] … a randomized, double-blind, placebo-controlled trial in which unblinding is common due to an effect of the test drug, and where a modest treatment effect is found on a primary endpoint that is subject to bias when drug assignment is known (e.g., a physician global impression). In these cases, the trials might not be considered adequate and well-controlled."

* International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline Statistical Principles for Clinical Trials E9 Current Step 4 Version.; 1998. https://database.ich.org/sites/default/files/E9_Guideline.pdf

^ Center for Biologics Evaluation and Research, Center for Drug Evaluation and Research. Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products. Guidance for Industry. U.S. Food and Drug Administration. Published December 2019. Accessed March 28, 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products

Dr. Suresh Muthukumaraswamy from the University of Auckland illustrated how unblinding and expectancy affect the causal inference assumptions underlying blinded randomized controlled trials.[19]

> **Given the obvious psychoactive effects of psychedelic drugs, those in the active intervention group will know they've received the treatment and therefore may show a greater treatment response due to expectancy effects. But those who are in the placebo intervention will know they've received the placebo, and disappointment may decrease the placebo response."** [20]

The combination of a disappointment response[21] plus expectancy effects[22] in the setting of unblinding can lead to overestimation of the effect size. When the blind is broken in a two-arm RCT, the ability to distinguish the treatment effect from the placebo expectancy effect is reduced.

Participants come to trials with expectations based on personal internalized experiences and social and cultural influences and beliefs. In the context of a clinical trial, expectancy is formed by the information shared—potential participants have expectations about the psychedelic experience, the therapeutic response and efficacy, and how they might benefit from the trial. Efforts should be made to assess and understand these expectancies. Examples of methods to mitigate expectancy and reduce bias in psychedelic clinical trials provided by Session 2 panel members are listed in Table 4. The use of a blinding questionnaire to determine if unblinding has occurred is highly recommended for all psychedelic studies.

> **I'd say if you can measure the unblinding and get maybe closer, so your unblinding rate is maybe not 99%, but down to like 60%, 70%, then you could potentially start to [do] stratification analysis and look at … whether your treatment effects still exists post-stratification. And that would start to provide evidence that requires us to get our designs a bit better so that we're a little bit less unblinded because you can already do that with antidepressant trials, for example. So this would be a move in the right direction."** — Dr. Suresh Muthukumaraswamy

19 RCTs meet causal inference assumptions by using randomization, sufficient sample size, allocation concealment, and double-blinding.

20 Muthukumaraswamy SD, Forsyth A, Lumley T. Blinding and expectancy confounds in psychedelic randomized controlled trials. Expert Rev Clin Pharmacol. 2021 Sep;14(9):1133-1152. doi: 10.1080/17512433.2021.1933434

21 Those participants that receive a placebo intervention may know they have received the placebo and disappointment may decrease their placebo response. Muthukumaraswamy S. Challenges for Psychedelic Clinical Trial Design; January 31, 2024. https://reaganudall.org/news-and-events/events/advancing-psychedelic-clinical-study-design

22 Given the obvious psychoactive effects of psychedelic drugs, those in an active intervention group likely know they have received the treatment and may show greater treatment response due to expectancy effects.

Table 4. Methods to Minimize Expectancy and Reduce Bias in Clinical Trials

- Drug blinding, therapist blinding, patient blinding
- Different in-session and post-treatment therapists
- Evaluators blinded to treatment and visit number
- Systematic treatment of patients in intervention and control groups (e.g., in-session therapy, psychological support)
- Administration of expectancy questionnaires to both participants and researchers before and after the treatment episode
- Information sheets to set realistic expectations and facilitator training with a neutral tone to minimize contributions to expectancy
- Review of patient-facing information to understand the impact on outcome expectancy

Measures of uncertainty also help to provide an understanding of how certain study participants are that they received a particular drug and dose or placebo. Even if unblinding occurs, measuring how certain a person is as to their treatment assignment provides additional information about how potential unblinding affects study outcomes.

ADDITIONAL CONSIDERATIONS

- How does expectancy or functional unblinding affect the durability of effect from a single dose?
- What do study participants think about having expectations met or not met from the clinical trial experience?

KEY POINTS: BLINDING & EXPECTANCY

- Standardized information is important to mitigate participant expectancy and reduce bias
- Measurement of blinding/unblinding is essential to study integrity
- De-blinded trials risk being unable to distinguish between treatment and placebo responses

C) EVALUATING DOSE-RESPONSE

EXCERPT FROM FDA GUIDANCE

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

Sponsors should plan to characterize the dose-response relationship for both safety and efficacy early in the drug development program.

The dose-response relationship for most psychedelic drugs is poorly understood,[23] thus research studies generating this data should establish:

- Doses that produce a psychedelic response,
- Doses that produce efficacy for a specific indication, and
- Doses that are safe to administer.

Examples of dose-ranging and dose-optimization study designs were presented during the workshop. Presenters also recommended reviewing historical studies to prevent repeating clinical trials for what is already known. Considerations for redosing include the duration of the treatment response after the initial dosing regimen, the efficacy of multiple administrations, and safety concerns both in the short and long term.

In addition to the psychedelic dose, the "dose" of psychotherapy or psychosocial support may be important to the dose-response relationship being studied. Additional research is needed to better understand the distinct and dynamic effects of a drug plus psychological intervention, which has particular implications for determining an appropriate medication dose. Further discussion of the integration of drug and psychotherapy is discussed under set and setting below.

> **"I think if you have the time and the money dose response curves are the way to go… How do these change with concomitant medications? There will always be individual differences with responders and non-responders. Even if we figure out a good average dose for each of these compounds, it's likely not going to be a one-size-fits-all approach…"** — Dr. Jennifer Mitchell

Dr. Carla Canuso from Johnson & Johnson described the regulatory pathway for approval of esketamine nasal spray for treatment-resistant depression as a case study from which insights may apply to psychedelic research and development programs. Key takeaways from this novel treatment paradigm included:[24]

- Treatments with novel mechanisms of action and new dosing paradigms will require unique clinical development plans to inform labeling and clinical use
- Durability of effect becomes an even greater factor in the overall benefit-risk assessment of novel therapeutics with safety and abuse liabilities
- Depending on how a treatment will be used, maintenance of effect studies may be required pre-approval
- Post-approval data collection can further inform durability of effect
- Collaborate early and often with regulators

ADDITIONAL CONSIDERATIONS

- How do doses established in research studies translate to clinical practice in a real-world setting?
- What are the consequences to repeated doses over months or years?

23 U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Psychedelic Drugs: Considerations for Clinical Investigations, Guidance for Industry, Draft Guidance. June 26, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/psychedelic-drugs-considerations-clinical-investigations

24 Canuso CM. Durability of Treatment Effect: Insights from the Esketamine Nasal Spray Treatment-Resistant Depression Program; January 31, 2024. https://reaganudall.org/news-and-events/events/advancing-psychedelic-clinical-study-design

KEY POINTS: DOSING

- Safe and effective doses are compound dependent; it's important to be specific rather than categorical about dose effects for each psychedelic, dose, and condition being studied
- What is the "dose" of psychotherapy or psychological support when provided in combination with a psychedelic?

D) ASSESSING DURABILITY OF TREATMENT RESPONSE

EXCERPT FROM FDA GUIDANCE

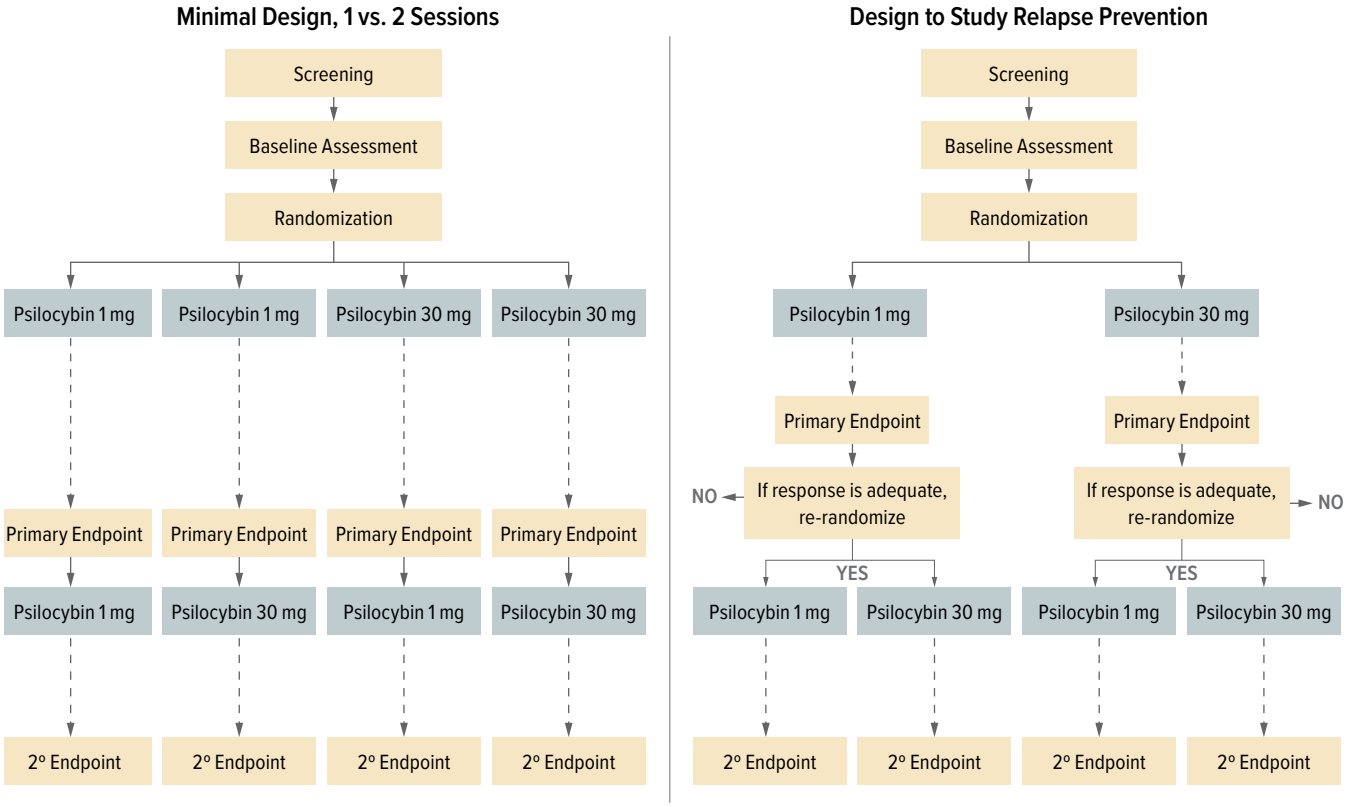
Sponsors should plan to characterize the durability of response for their drug product, the recommended interdose interval for maintenance of effect, and the safety and efficacy of repeat dosing. At a minimum, for the treatment of a chronic illness such as post-traumatic stress disorder or major depressive disorder, sponsors should evaluate the effect of treatment at 12 weeks. However, sponsors should continue to follow subjects in an open-label extension period for a year beyond the Week 12 endpoint to monitor for symptom recurrence or, potentially, the need for repeat dosing.

Single or short-term doses are hypothesized to produce long-term (e.g., weeks to years) effects. Duration of treatment effects depends on the drug, dose, number, and schedule of doses, indication, patient characteristics, and concomitant treatment.[25] For episodic disorders, like depression, it is essential to distinguish between the durability of the treatment effect during the initial treatment episode and the maintenance of the treatment effect to prevent relapse, or to treat a relapse or recurrence. Whether repeat dosing improves efficacy without also increasing toxicity or adverse effects (i.e., via accumulative risk with repeated exposure to the drug) remains to be seen.

In order to adequately study the dose and durability of treatment response, more complex study designs are required. Figure 1 depicts study designs presented by Dr. Bogenschutz from NYU Langone Center for Psychedelic Medicine, that may be useful in determining the durability of psychedelic drug effects.

25 Bogenschutz MP. Some thoughts on durability of psychedelic treatment response; January 31, 2024. https://reaganudall.org/news-and-events/events/advancing-psychedelic-clinical-study-design

Figure 1. Examples of Potential Study Designs to Address Durability of Effects[26]



An important consideration when studying durability of treatment is the phenomenon of a patient appearing to worsen clinically before they get better. This makes timing and frequency of efficacy assessments vital when measuring outcomes, as discussed in the next section.

ADDITIONAL CONSIDERATIONS

- How can we maximize the durability of the effects of a treatment episode?
- When is redosing indicated and what are the criteria for redosing?
- How should we decide if and when follow-up treatment should be administered?
- Does blinding become less of an issue if there is strong durability of effects?

KEY POINTS: DURABILITY OF TREATMENT RESPONSE

- Studies need to take into account the time course and potential outcomes (e.g., both positive and negative experiences) of a therapeutic response when assessing durability
- Studies should distinguish between durability of treatment effect during the initial treatment episode and maintenance of treatment effect related to relapse or recurrence

26 Ibid.

E) DEFINING OUTCOMES

Given the challenges discussed above, how do researchers need to characterize the safety and effectiveness of psychedelics?

EXCERPT FROM FDA GUIDANCE

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 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 effects of psychedelics are not predetermined and not universal. Measurement of a mystical experience, which may include both positive and negative experiences and emotions, is not a common endpoint in medicine or regulatory science. Difficult experiences during the treatment episode or shortly after may be a part of the treatment effect rather than an adverse effect. As with many psychiatric conditions, a patient may appear to be worse before they get better, which makes the timing of efficacy assessments important.

Clear definitions of outcome measures are essential when conducting psychedelic clinical studies. As such, it is necessary to clearly state how and at what frequency efficacy and safety outcomes are measured. As mentioned earlier, a difficult experience may be a sign of efficacy or may be an adverse effect. How these data are collected, interpreted, and reported needs to be delineated at the outset of a trial. It is vital to define how difficult experiences will be characterized in a study and to be specific about safety parameters for each drug and not broadly apply categories of adverse experience across psychedelics.

> “So, I do think we have to carefully consider the time course of the therapeutic response and note that certain outcomes that we might think of as adverse events could in fact represent a therapeutic process that would play out over time.” — Dr. Peter Hendricks

Set and Setting Considerations

Psychedelic experiences are defined by context, both internal and external. The mindset of the participant prior to and after the psychedelic session (set) and the physical setting and activities that the participant engages in during their psychedelic session shape the psychedelic experience (setting).

Whether a unique synergy exists between a psychedelic drug and psychotherapy, and the degree to which therapy may influence efficacy, is not well-defined by the literature. Standardization of the elements of psychological support provided to both the treatment and control groups reduces the risk of bias that may be introduced by supportive care. In order to determine which features of set and setting are critical for efficacy and to ensure safety, research will need to be conducted using well-done factorial studies.

Elements of set and setting, as defined and presented by Dr. Ido Hartogosohn from Bar-Ilan University, are outlined in Table 5. These elements may affect outcomes and should be accounted for, as much as possible, in psychedelic clinical study designs. How orientation and integration sessions, to support a subject in a clinical trial, contributes to safety and efficacy also needs to be considered.

Table 5: Elements of Set & Setting[27]

SET	SETTING
The mindset of the participant prior to and after the psychedelic session and the role of psychotherapy in shaping the mindset	The physical setting and activities participants will engage in during their psychedelic session
Considerations • Personality • Expectancy • Intention • Substance & dose • Skillset	Considerations • Physical (sensory) environment • Social context • Cultural context • Session • Integration/Matrix

> "And on the collective level, the resurgence of psychedelics beckons us to consider how these social and cultural landscape of today's society shapes the set and setting in clinical trials and applications."
> — Dr. Ido Hartogsohn

Table 6, from Johnson, et. al. and presented by Dr. Farchione from the FDA, provides examples of psychedelic psychotherapy features that may contribute to efficacy and need further study to determine how these components affect (or do not affect) measured study outcomes.

Table 6. Example Psychedelic Psychotherapy Components[28]

PREPARATORY PSYCHOTHERAPY	DRUG TREATMENT SESSION	INTEGRATIVE PSYCHOTHERAPY
• Series of meetings (e.g., 4 x 2-hour sessions in month prior to drug treatment) between patients and monitors/ therapists • Discuss meaningful life experiences, beliefs, goals	• Monitors/therapists offer gentle guidance, support, and reassurance as needed • Encouragement to "trust, let go, be open" to experience • Instrumental music, eyeshades to block distractions	• Series of meetings (e.g., next-day session + 2 additional sessions over 6 months) between patients and monitors/therapists • Discuss novel thoughts and feelings that arose during drug treatment session
Goal: Prepare patient for drug treatment, build trust/rapport, establish intentions/goals	**Goal:** Reduce adverse psychological reactions, facilitate therapeutic session	**Goal:** Ensure psychological stability, process and integrate experience

27 Hartogsohn I. Contextual considerations in clinical trials and applications; February 1, 2024. https://reaganudall.org/news-and-events/events/advancing-psychedelic-clinical-study-design

28 Johnson M, Richards W, Griffiths R. Human hallucinogen research: guidelines for safety. J Psychopharmacol. 2008 Aug;22(6):603–20. doi: 10.1177/0269881108093587

In addition to the psychotherapy or psychological support component in psychedelic clinical research, defining the cultural context in which the study is being conducted is essential. Ensuring that study populations have adequate diversity is crucial to proper drug evaluation.

Regulatory Considerations for Set and Setting

Set and setting may be important for drug optimization and ensuring safety (i.e., mitigating unpleasant experiences and possible side effects). As discussed under the FDA Prescription Drug Regulatory Authority section, the FDA does not regulate the practice of medicine but may require elements to assure safe use which may be influenced by set and setting, in order to write a product label.

ADDITIONAL CONSIDERATIONS

- What are the expected clinical responses for each drug studied?
- How are adverse effects defined in this space?
- Do more monitors increase safety?
- How might risk mitigation strategies used in clinical trials translate into clinical practice?
- How do set and setting influence the psychedelic experience?

KEY POINTS: DEFINING OUTCOMES AND SET & SETTING

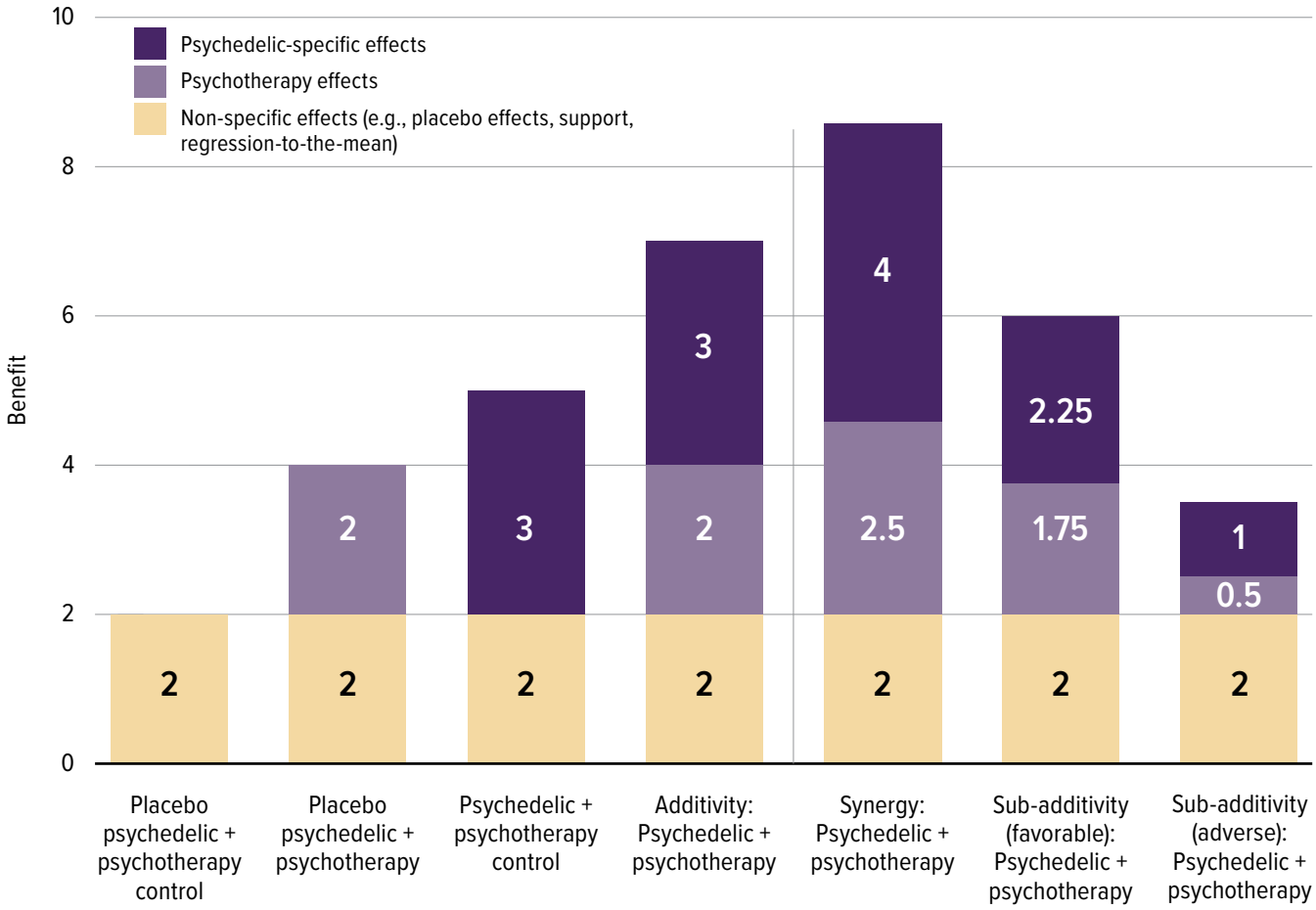
- Efficacy and safety measures, and appropriate intervals of measurement, need to be clearly defined
- Social and cultural context or experiences may affect the selection of study participants and study results, and therefore the generalizability of study findings
- The "dose" of psychotherapy or psychological support provided in combination with a psychedelic, needs to be defined and measured

F) CHARACTERIZING THE CONTRIBUTION OF PSYCHOTHERAPY

Factorial study designs are ideal to understand the relative contribution and/or synergistic effect of psychotherapy and psychedelic treatment. Figure 2, adapted from Dworkin, et. al., is an example of an RCT with a factorial design that assesses the individual and possible synergistic effects of treatments.[29] Potential study designs to address durability of effects were presented earlier.

29 Dworkin RH, McDermott MP, Nayak SM, Strain EC. Psychedelics and Psychotherapy: Is the Whole Greater than the Sum of its Parts? Clin Pharmacol Ther. 2023 Dec;114(6):1166–1169. doi: 10.1002/cpt.3050. Epub 2023 Oct 5.

Figure 2: RCT with a Factorial Design



(i) The first 4 columns reflect the cells of a 2 × 2 factorial clinical trial of a psychedelic (with placebo control) and psychotherapy (with psychotherapy control). The placebo control could be either inert or active; the psychotherapy control would include sufficient support to minimize harms; (ii) the numeric values of "benefit" on the y-axis are selected for illustrative purposes; (iii) again, for illustrative purposes only, the magnitude of the psychedelic benefit is greater than the magnitude of the psychotherapy benefit; similarly, the effects of synergy and subadditivity on these benefits differ for the psychedelic and for psychotherapy; (iv) synergy (fifth bar from left) occurs when combining a psychedelic and psychotherapy produces greater benefit than what would be expected from adding the benefits of the two components (as in the fourth bar from the left); (v) subadditivity (sixth bar from the left) is favorable when the benefit of the combination is greater than the effects of each of its components; (vi) subadditivity (seventh bar from the left) is adverse when the benefit of the combination is less than (or equal to) the effects of each of its components.

4. Future Directions

Panelists discussed considerations for potential psychedelic use in the real world, with the understanding that as of June 2024, no psychedelic drug has been FDA-approved. It is important to distinguish between the state-level legal status of psychedelics and the federal Controlled Substances Act, which makes Schedule I drugs like LSD, psilocybin, and MDMA illegal to use in all states, outside of FDA-authorized clinical studies. Topics reviewed included potential implementation strategies to integrate psychedelics into clinical care, data needs and surveillance for assessing long-term safety and effectiveness, and public messaging and education considerations related to psychedelics.

Panelists noted that if a psychedelic drug is approved by the FDA, implementation of this type of newly approved treatment will require coordination at the federal, state, and facility levels. Implementation plans and workflow restructuring, infrastructure considerations (e.g., staffing models, clinical space, setting), and insurance coverage considerations will require coordination among stakeholders to facilitate appropriate and equitable access to a new treatment paradigm. Stepwise implementation in an iterative type of learning environment is going to be critical in the rollout of psychedelic clinical programs that will likely look different from current outpatient mental health settings.[30] Dr. Ilse Wiechers from the VHA Office of Mental Health and Suicide Prevention in the Department of Veterans Affairs described two key lessons learned during the successful rollout of the VA's esketamine and ketamine programs that may be applicable to the future clinical implementation of psychedelics.

> **"One of the keys to our success has been collaboration early and often across the many service lines at a facility or regional level with our program offices … the other thing that I think was important … was a stepwise implementation plan, building upon areas where we had existing expertise … so we could learn from implementation, from people who had existing expertise first, really establish our solid best practices, and then use those and expand those outward."** — Dr. Ilse Wiechers

In the potential event that a psychedelic drug is approved by the FDA, panelists stated that adverse event surveillance would be complicated by the presence of psychedelics in both the legal and non-medical drug supply. To protect public health, consumer education about how to distinguish between an FDA-approved product, use of a state-sanctioned but federally illicit product, or recreational illicit use of either product is necessary. Unsupervised and uncontrolled use of psychedelics can cause harm.

> **"… our public acceptance and public interest [in psychedelics] is ahead of the science… we really don't understand the right dose, the right frequency, the right setting and psychotherapies to use. We don't know how long effects will last and for whom, but we do know that between 2018 and 2022, in California, there was a 54% increase in people with problems who've taken psychedelics showing up in the emergency room.[31] We do know that there has been an increase in admissions people that were taking psychedelics."** — Dr. Mark Rapaport

Education and management of expectations will be needed for both consumers and health care professionals.

> **"I don't think we can prevent people from using [psychedelics] at this point so to the extent that we can educate them [is paramount] … And I think FDA has a great role to play there in its information providing capacity."** — Dr. Mason Marks

30 Wiechers I. Considerations for Potential Psychedelic Use in the Real World; February 1, 2024. https://reaganudall.org/news-and-events/events/advancing-psychedelic-clinical-study-design

31 Garel N, Tate S, Nash K, Lembke A. Trends in hallucinogen-associated emergency department visits and hospitalizations in California, USA, from 2016 to 2022. Addiction. 2024 Jan 11. doi: 10.1111/add.16432

5. Conclusion

Psychedelics represent a potential new paradigm in the treatment of many disorders including psychiatric disorders. In June 2023, the FDA issued its first draft guidance for the industry addressing challenges in the development of psychedelic-based therapeutics. Participants in this workshop discussed some of these challenges including critical elements of trial design, functional unblinding, dosing paradigm, timing of assessment of efficacy outcomes, and the role of supportive non-pharmacological therapy. Although clinical research and regulatory science have made progress, there are still many unanswered questions. Adequate well-designed studies providing robust data and multi-stakeholder collaboration are imperative to move the science forward.

Appendix: Agenda

Advancing Psychedelic Clinical Study Design

Wednesday, January 31 from 10 am to 2 pm ET
Thursday, February 1 from 10 am to 1 pm ET
Virtual Public Meeting

AGENDA

Meeting Description

The Reagan-Udall Foundation for the FDA, in collaboration with the FDA, is hosting a virtual public workshop to bring together researchers, regulated industry, and other key stakeholders to discuss scientific issues that arise while working with psychedelics in clinical trials and drug development. In June 2023, FDA issued its first draft psychedelics guidance for industry, *Psychedelic Drugs: Considerations for Clinical Investigations*, to provide general considerations to sponsors developing psychedelic drugs for treatment of medical conditions (e.g., psychiatric disorders, substance use disorders). While the guidance highlights some of the challenges in designing clinical trials with psychedelics capable of yielding interpretable results, many questions remain about the most appropriate way to address these challenges. This workshop will explore empiric approaches to address key issues in psychedelic drug development and research.

Meeting Goals

1. Understand the experiences of scientists working with psychedelics in FDA-authorized clinical studies and drug development
2. Explore considerations for psychedelic clinical trial designs
3. Explore perspectives and current research on set and settings in psychedelic clinical trials
4. Provide an overview of the June 2023 draft FDA guidance for industry: Psychedelic Drugs: Considerations for Clinical Investigations

DAY 1: JANUARY 31, 2024

10 am	**Welcome**
	Speaker: Susan C. Winckler, RPh, Esq Reagan-Udall Foundation for the FDA
10:05 am	**Opening Remarks**
	Speaker: Patrizia Cavazzoni, MD, U.S. Food and Drug Administration
10:15 am	**Session 1: Overview of FDA's Psychedelics Clinical Investigation Guidance**
	This session will provide a brief overview of the June 2023 draft FDA guidance for industry: *Psychedelic Drugs: Considerations for Clinical Investigations* **Speaker:** Tiffany Farchione, MD, U.S. Food and Drug Administration
10:40 am	**Session 2: Psychedelics Study Design, Control Conditions, and Blinding**
	This session will focus on challenges in selecting control conditions to create blinding for psychedelic studies, to reduce bias and to determine whether changes in outcome measures can be attributed to the psychedelic. **Speakers:** • Suresh Muthukumaraswamy, PhD, University of Auckland • Franz Vollenweider, MD, University of Zürich **Respondents:** • Matt Butler, MD, King's College London • Michael Davis, MD, PhD, Usona Institute • Bernard Fischer, MD, U.S. Food and Drug Administration
11:40 am	**Break**
11:50 am	**Session 3: Dosing**
	This session will focus on issues related to psychedelic drug dosing (dose-response, single vs. repeat dosing, microdosing, etc.) in three substance areas: MDMA, Psilocybin, and LSD. **Speakers:** • Robert Barrow, MSc, MindMed • Guy Goodwin, DPhil, Compass Pathways • Berra Yazar-Klosinski, PhD, Lykos Therapeutics **Respondents:** • Peter Hendricks, PhD, University of Alabama at Birmingham • Jennifer Mitchell, PhD, University of California, San Francisco • Martine Solages, MD, U.S. Food and Drug Administration

1 pm	**Session 4: Durability of Treatment Response**
	This session will focus on the durability of the psychedelic therapeutic response and discuss the conditions under which additional treatment should be considered. **Speakers:** • Michael P. Bogenschutz, MD, NYU Langone Center for Psychedelic Medicine • Carla Canuso, MD, Johnson & Johnson Innovative Medicine **Respondents:** • Valentina Mantua, MD, PhD, U.S. Food and Drug Administration • Charles L. Raison, MD, University of Wisconsin-Madison
2 pm	**Adjourn Day 1**

DAY 2: FEBRUARY 1, 2024

10 am	**Welcome**
	Speaker: Susan C. Winckler
10:10 am	**Session 5: Set and Setting**
	This session will focus on set (the mindset of the participant prior to and after the psychedelic session, the role of psychotherapy) and setting (the way the session room is designed, activities during the psychedelic session). **Speakers:** • Ido Hartogsohn, PhD, Bar-Ilan University • David Yaden, PhD, Johns Hopkins University **Respondents:** • Brian Anderson, MD, University of California, San Francisco • Javier Muniz, MD, U.S. Food and Drug Administration
11:20 am	**Session 6: Overview of FDA Regulatory Authority**
	This session will provide an overview of the limits of FDA authorities after a new drug application for any drug product is approved. **Presenter:** • Tiffany Farchione
11:40 am	**Session 7: Considerations for Potential Psychedelic Use in the Real World**
	This session will include a discussion focused on understanding current use and considerations for potential future use of psychedelics. **Speakers:** • Richard C. Dart, MD, PhD, Denver Health and Hospital Authority • Mason Marks, MD, JD, Harvard Law School • Mark H. Rapaport, MD, University of Utah School of Medicine • Lisa Robin, MLA, Federation of State Medical Boards • Marta Sokolowska, PhD, U.S. Food and Drug Administration • Ilse Wiechers, MD, MPP, MHS, U.S. Department of Veterans Affairs
12:55 pm	**Closing Remarks**
	Susan C. Winckler
1 pm	**Adjourn Day 2**

1333 New Hampshire Ave, NW
Suite 420
Washington, DC 20036

reaganudall.org