Unlocking the complexities of psychedelic clinical trials and FDA's approach to guidance

On June 23, 2023, the US Food and Drug Administration (FDA) published new draft guidance, **Psychedelic Drugs: Considerations for Clinical Investigations, Guidance for Industry**, for researchers studying the use of psychedelic drugs for the potential treatment of medical conditions, including psychiatric and substance abuse disorders.

The much-needed draft guidance offers the pharmaceutical industry the clearest yet understanding of the agency's interest in, and concerns about, how clinical research is performed with psychedelic substances – most notably psilocybin, lysergic acid diethylamide (LSD) and methylenedioxymethamphetamine (MDMA).

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Whitepaper

While nothing in the guidance should be especially surprising to those closest to research into psychedelic substances and FDA's general approach to drug evaluation, it is nonetheless valuable to have such a clear understanding of the agency's specific expectations for future study designs.

The FDA invited public comment to provide feedback on these recent guidance. Here we offer our thoughts on the agency's initial guidance and summarize key points for Sponsors to consider as they pursue research in this area and seek FDA approval.

The Purpose of the Guidance: Preparation for Future Drug Applications

FDA's guidance is timely in that "In recent years, interest in the therapeutic potential of psychedelic drugs has been increasing."[1] Indeed, the National Institute on Drug Abuse reports that the National Institutes of Health (NIH) are funding more than 70 projects studying the use of psychedelics as therapy, as of July 2023.[2] This is remarkable given that there were no such projects funded by the NIH between 2006 and 2020.[3]

A growing number of biotech companies are also conducting research into psychedelics as therapeutics, with the psychedelic market forecasted to grow with a CAGR of 16.3 percent between 2020 and 2027.[5]

The director of the Division of Psychiatry in FDA's Center for Drug Evaluation and Research (CDER), Dr. Tiffany Farchione, stated,

> "By publishing this draft guidance, FDA hopes to outline the challenges inherent in designing psychedelic drug development programs and provide information on how to address these challenges. The goal is to help researchers design studies that will yield interpretable results that will be capable of supporting future drug applications."[6]

Those challenges include perceptual disturbances and alterations in consciousness that can last for several hours as well as the frequent need to incorporate psychological or behavioral intervention. The guidance states, "These and other unusual characteristics should be considered when designing clinical studies so that the results of those studies can be interpretable."

Importantly, the agency acknowledges that the guidance is not all-inclusive; rather it presents "foundational constructs" that should be considered.

A Uniform Message: Potential, but More Work to Do

US federal agencies appear to be speaking with one voice when it comes to interest in psychedelic drugs as potential therapies. We interpret their comments and actions as sending the message that while this area of research holds promise, rigorous evidence is needed to demonstrate conclusively that psychedelics are safe and effective.

The evidence standards are the same as for any other investigational drug, and ensuring that trials are "adequate and well controlled" is particularly challenging in this area.

Dr. Farchione stressed,

> "Psychedelic drugs show initial promise as potential treatments for mood, anxiety and substance use disorders. However, these are still investigational products."

This caution was echoed by the Director of the National Institute on Drug Abuse (NIDA), Dr. Nora Volklow, and the Director of the National Institute of Mental Health (NIMH), Dr. Joshua Gordon, as they offered this view:

> "Overall, the therapeutic evidence for classic psychedelics remains limited and... much remains unknown about how psychedelic compounds work, how to administer them most effectively and safely, and how to identify which patients are the best candidates and which are at risk of adverse outcomes."[7]

Study Challenges Highlighted by the Guidance

Design Issues

Unblinding can occur with a single incidence of observing a dosing session based on the subject's behavior. The guidance suggests that it is therefore important not to have the in-session monitor involved in post-session psychotherapy "because their knowledge of the treatment could bias the delivery of subsequent therapy."

Also, many studies are designed to test an integrated treatment model whereby the patient receives psychotherapy prior to the substances administration (to prepare for the experience properly) and then psychotherapy post treatment (to support the patient in behavioral changes, etc.).

In the process, a therapeutic alliance is built between the psychotherapist and the patient. The intent of such study designs is to mimic the paradigm of how psychedelic substances would likely be administered in the real world.

This poses a challenge, though, in that it becomes difficult to isolate the effect of the psychedelic from that of the psychotherapy. For this reason, the guidance states:

> 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 overall treatment effect. A factorial design may be useful for characterizing the separate contributions of drug and psychotherapy to any observed treatment response.

Because events such as hallucinations are expected during dosing sessions, in addition to the risk and implications of facilitators being unblinded, it is likely that collecting these events as AEs increases the possibility of inadvertent unblinding of study team members with access to accumulating safety data throughout the study.

While the guidance does not offer suggestions for overcoming this challenge with placebo-controlled designs, it is clearly an area for further brainstorming and discussion.

Safety Issues

Researchers must demonstrate that these drugs are not drugs of abuse. The requirements around this are not new and are fully outlined in companion guidance, **Assessment of Abuse Potential of Drugs**. The agency's emphasis on this is unmistakable.

The guidance offers perhaps the greatest level of detail around the need for two monitors during dosing sessions, with descriptions of the qualifications required. FDA clearly expects safety monitoring to be robust and in-person.

Reporting Issues

The guidance states:

> 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. Thus, for all 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.

However, there currently is no established, standardized mechanism for defining and distinguishing expected events (hallucinations) from those that are more medically significant, such as hallucinogenic persisting perception disorder.

Key Takeaways for Sponsors

1

Consult with FDA

FDA's guidance document is a useful roadmap that can help Sponsors focus on the areas that are highlighted as being of particular interest to FDA. It does not, however, obviate the need to consult with the agency at a pre-IND meeting to discuss the feasibility and acceptability of your planned approach. The guidance does not cover every conceivable situation/question; indeed, it is billed as presenting "foundational constructs" only.

We recommend that Sponsors use this draft guidance to inform conversations with FDA leading up to any new study using psychedelics. There are challenges to be considered for all psychedelic studies, and it is likely that Sponsors will have study-specific questions and concerns related to details within the guidance document. These would be important discussion points for a pre-IND meeting with FDA, for example. Having these early discussions will be helpful for any sponsor to optimize the extent to which planned research will speak to the priorities laid out in the guidance.

Also, as the guidance does not define "chronic dosing," Sponsors should include this as part of their discussions with FDA in the context of the investigational drug and treatment model under discussion. It would be important to have this clarified early in the development program to inform both early- and late-phase studies.

2

Think Outside the Box

There remains a need to surmount the challenges posed by the fact that functional unblinding is difficult to avoid in placebo-controlled trials involving psychedelics. Careful consideration of this element of study design is critical in the early development process for a given protocol. FDA has suggested that alternatives to inert placebo, such as subperceptual doses of the psychedelic agent under investigation, may offer a way to mitigate the potential effects of functional unblinding. Yet, as noted by FDA, use of alternatives to inert placebo introduces challenges to the ability to interpret and evaluate safety events that may occur over the course of a study.

We agree with FDA's recommendations encouraging Sponsors to consider complimentary trial designs across multiple protocols. It may also be possible to address some of these challenges in the study design for a single protocol. For instance, one could design a study that investigates the intervention's effect as a within-subject factor as opposed to between-subjects. Wait list crossover studies come to mind as a way this might be done, provided FDA is accepting. Such designs have the advantage of potentially requiring fewer patients than a parallel design that compares treatments. There are downsides, however, which include the potential for "differential attrition" between the cohorts and the potential for "demoralization" of the group that is to receive their intervention later.[8]

We strongly recommend that Sponsors include these considerations in early conversations with FDA.

3

Measure Abuse Potential

The guidance stresses the criticality of assessing the abuse potential of these drugs and complying with companion guidance on the subject when designing clinical trials in this space. It is advisable to have these guidance recommendations top of mind during all stages in the development process.

Key Takeaways for Sponsors Continued

3

Measure Abuse Potential Continued

To support the recommendation that abuse-related AEs be reported with narratives to adequately capture clinical context and evaluation of any such events, we suggest that capturing safety events as "Events of Special Interest" provides a format that allows narratives from investigators on their interpretation of events to be included. These details/clinical interpretations will be important in addressing FDA's concerns about distinguishing between expected events and those that are more medically significant (such as hallucinogenic persisting perception disorder).

We recommend that data be collected using a strategy that standardizes the evaluation of potential abuse events. The Timeline Followback (TLFB) tool is one such possibility which has been shown to improve recall by "avoiding the need for respondents to aggregate behaviors over broad recall intervals."[9]

4

Address the Potential for Bias

FDA also notes that psychotherapeutic interventions "have the potential to increase expectancy and performance biases." In the draft guidance, the agency indicates that Sponsors should be prepared to speak robustly to a justification for including a psychotherapy component in a study design. In addition, Sponsors should be prepared to speak to how their study design aims to reduce bias, or to "quantify the contribution of psychotherapy to the overall treatment effect." A well-thought-out statistical approach, initiated early in the planning process, will greatly assist any Sponsor in thinking through how to optimize the study design to address some of the suggestions offered in this guidance. While bias is not limited to trials involving a psychotherapy component, in this field of research, it is particularly helpful to rely on the experience and counsel of a CRO with relevant statistical experience in the field of psychedelic research.

5

Develop a Robust Plan for Monitoring Dosing Sessions

While it remains to be seen if FDA will cede any ground on the requirement that two monitors be present for the dosing session, it is worth asking if there are any situations/conditions under which both monitors might not need to be present. What about when the study is administering subperceptual doses? Under any circumstances could monitoring occur remotely by video? If the need to have two monitors present in the dosing session is non-negotiable, this requirement becomes an operational challenge in the pre-approval setting for Sponsors in finding sites that are properly staffed to accommodate this requirement. Sites must be properly vetted with this in mind.

As the guidance does not list the responsibilities of those observers, it would behoove Sponsors to carefully consider what each observer would be tasked with doing what and include that detail in their protocol and/or study plans (e.g., Manual of Procedures).

Monitors have an integral role as observers of potential AEs, so it is important to define a reporting mechanism/communication workflow so that events during dosing are properly communicated to appropriate site staff for AE reporting. Also, because monitors are more likely to be able to identify the treatment assignment because of the nature of the investigational product, not having in-session monitors involved in the collection/assessment of efficacy outcome measures is critical.

Conclusion

Given the growing interest in exploring the therapeutic potential of selected psychedelic substances, FDA's publication of draft guidance for industry is both timely and welcome. The document outlines general principles to be followed and calls out specific issues that must be addressed to ensure that trials of psychedelics are "adequate and well controlled."

We believe the issues, while challenging, are surmountable through consultation with the agency and with the support of experts within a Contract Research Organization (CRO) having both statistical and operational experience in psychedelic research.

References and Resources

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