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THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

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22 August 2023

To: Food and Drug Administration, HHS

Re: Docket No. FDA-2023-D-1987

**COMMENTS ON:**

**PSYCHEDELIC DRUGS: CONSIDERATIONS FOR CLINICAL INVESTIGATIONS, GUIDANCE FOR INDUSTRY**

The ISCTM thanks the FDA for the opportunity to comment on the draft guidance Psychedelic Drugs: Considerations for Clinical Investigations, Guidance for Industry. The ISCTM formed a working group to review and provide comments on behalf of the Society. This working group was chaired by Drs. Amir Inamdar and Joyce Tsai. The authors (in alphabetical order) of the comments provided below are:

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The comments represent the opinions of the working group participants but not necessarily institutions with which they are affiliated.

**General Comments**

It is understood that the FDA draft guidance presents recommendations regarding foundational concepts that should be considered in the design and execution of clinical trials investigating the effectiveness and safety of psychedelic drugs for the treatment of medical conditions. The ISCTM thanks the Division of Psychiatry in the Center for Drug Evaluation and Research at the Food and Drug Administration for this guidance, as it comes at a time when research and interest in this area are growing rapidly yet there is no consensus on the issues that are critical to good clinical trial methodology in psychedelic drug research.

The ISCTM looks forward to the evolution of guidance as clinical experience in this area is generated; and is prepared to, and would readily participate in, further public debate to achieve this goal.

Throughout this document, additional suggestions or modifications for text are inserted in regular font after italicized draft guidance text.

***I. INTRODUCTION***

No comments.

***II. BACKGROUND***

No comments.

***III. DISCUSSION***

**A) Chemistry, Manufacturing, and Controls**

**B) Nonclinical**

Line 138 states, *If a psychedelic drug is shown to be an agonist at 5-HT2B receptors, a thorough microscopic evaluation of the heart should be conducted to assess for potential heart valve thickening in both rodent and nonrodent repeat-dose toxicity studies, including sectioning of all heart valves.*

ISCTM notes that for valvulopathy associated with 5-HT2B agonism, a binding threshold is unknown and 5-HT2B receptor expression is variable between individuals. Given the limited published information available regarding these questions and the variety of dosing paradigms that could be implemented in the clinic (e.g., a few doses, multiple microdoses, etc.) the ISCTM notes that there is insufficient evidence to provide a more specific guidance, for example with respect to receptor binding thresholds. However, the ISCTM requests the agency to provide clarity on whether this guidance refers to a full agonist or a partial agonist.

**C) Clinical Pharmacology**

Line 162 states,
*Known pharmacodynamic interactions to consider include the following:*
*– Chronic use of selective serotonin reuptake inhibitors or monoamine oxidase inhibitors may reduce the effect of psychedelic drugs.*

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

There are limited and conflicting data that indicate a reduction of psychedelic effects with chronic administration of SSRIs. Where these data are available, they are inconclusive. Further, while acute use of monoamine oxidase inhibitors may potentiate psychedelic effects by preventing metabolism of most psychedelics, there are in fact data supporting better tolerability with acute concomitant use of SSRIs (e.g., Becker, 2021). The ISCTM therefore proposes rewording lines 162 through 169, as follows:

Pharmacodynamic interactions to consider include the following:
– The effect of chronic use of selective serotonin reuptake inhibitors on classic psychedelics (5HT2A agonists) is not established.

– Acute use of monoamine oxidase inhibitors use may potentiate psychedelic effects.

**D) Abuse Potential Assessment**

Line 187 states, *Many psychedelic drugs are Schedule I substances under the Controlled Substances Act because they have high abuse potential and …*

The ISCTM acknowledges that these drugs can be used recreationally, even though they may not be addictive in the classical sense (i.e., resulting in craving, dependence, withdrawal, etc.). Recreational use varies among these drugs and not all psychedelics have the same degree of recreational use. Therefore the use of the word ‘high’ in this guidance makes a generalization that may not be applicable to all psychedelics and may discourage potential investigators from participating in these trials. We therefore recommend that “high” be removed and the text is reworded as follows:

Many psychedelic drugs are Schedule I substances under the Controlled Substances Act because they have abuse potential and …

Line 210 states, *When appropriate, sponsors should propose the use of scientifically valid, published investigations to support the abuse potential assessment.*

The ISCTM recommends this be reworded as:
When appropriate, sponsors should propose the use of rigorous and scientifically valid, published investigations to support the abuse potential assessment.

**E) Clinical**
Line 274 states, *those who receive a placebo in the context of high expectancy may experience a nocebo effect (i.e., worsening of symptoms as a result of knowing they did not get active treatment).*

The ISCTM respectfully disagrees with the description of a 'nocebo effect'. A nocebo effect normally refers to adverse events in light of negative expectations. Worsening of symptoms without negative expectations is typically characterized as an adverse event. We recommend rewording as follows:

…those who receive a placebo in the context of high expectancy may experience a nocebo effect (i.e., develop adverse events due to believing they have received a psychedelic drug).

Line 283 states, *Sponsors should consider the use of video or central raters blinded to treatment allocation and visit number.*

The use of central blinded raters is generally to improve inter-rater reliability. That use of video or centralized blinded raters would improve blinding in psychedelic studies is an assumption that is not supported by currently available data, which are often mixed. Engagement of a service to provide video or centralized ratings adds to study complexity, cost, and burden. Alternative approaches to ensure blinding could be employed and assessed; data from the multiple approaches could then better inform the field as to the most appropriate methods.

The ISCTM therefore recommends rewording as follows:
Sponsors should consider the use of video or central raters, or utilize alternative approaches, to ensure that raters are blinded to treatment allocation and endpoint visit for primary endpoint assessment.

Line 288 states,
*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.*

We agree that a true placebo control is appropriate for assessment of safety. The proposed text however implies that a dose-response relationship might be expected in the case of efficacious psychedelic drugs. Historically, studies of drugs to treat psychiatric conditions have not consistently shown dose-response relationships. Currently available data from large, controlled studies of classic psychedelic drugs are too limited to support an assumption of a dose-response relationship to efficacy outcomes across the range of conditions for which these drugs are being tested and the limitations of currently accepted scales for assessing efficacy with psychedelics.

The ISCTM therefore recommends rewording as follows:
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 placebo-controlled trial may raise concerns about functional unblinding but would allow for better characterization of safety signals.

Line 308 states, *A factorial design may be useful for characterizing the separate contributions of drug and psychotherapy to any observed treatment response*.

It may be possible to separate the effects of drug from psychotherapy on treatment response by using a combination of studies, instead of a factorial design. The ISCTM therefore recommends rewording as follows:

A factorial design in some circumstances may be useful for characterizing the separate contributions of drug and psychotherapy to any observed treatment response.

Line 312 states, *The therapist monitoring the session can usually deduce the treatment assignment by observing the subject's behavior. Therefore, it is preferable that the in-session monitor is not involved in post-session psychotherapy because their knowledge of the treatment could bias the delivery of subsequent therapy.*

Continuity of clinician for the participant is the preferred model to deliver adequate psychological support. An important component of that psychological support, the purpose of post-treatment integration session(s), is to facilitate the patient's reflection on his/her subjective experience during the administration session. Hence, the assumption that a different therapist would remain blinded is incorrect. Instead, the therapist providing psychological support should not participate in any efficacy ratings or otherwise influence those who conduct such assessments. The ISCTM therefore recommends rewording as follows:

The clinician monitoring the session can usually deduce the treatment assignment by observing the subject's behavior. Therefore, it is preferable that the in-session monitor is not involved in post-session ratings or assessments because their knowledge of the treatment could bias the assessments.

Line 319 states, *Subjects receiving active treatment with psychedelic drugs remain in a vulnerable state for as long as 12 hours*.

Duration of 12 hours for post-treatment vulnerable state may not be true for the shorter-acting psychedelics such as 5-MeO-DMT, DMT or psilocin. Further, clinical monitoring may not be required for sub-psychedelic doses or microdoses. The ISCTM therefore recommends rewording as follows:

Subjects receiving active treatment may require clinical monitoring for an appropriate duration, depending on the pharmacokinetic and pharmacodynamic properties of the psychedelic drug being investigated.

Line 324 states, *Observation by two monitors for the duration of the treatment session*.
The ISCTM acknowledges the need for patient safeguarding and that two monitors may reduce the risk of abuse during the treatment session while patients are in a vulnerable mental state. However, for operational flexibility, the ISCTM requests that the wording be amended as follows:

Observation by two monitors for the duration of the treatment session; the assistant monitor may monitor via video.

Line 326 states, *A healthcare provider with graduate-level professional training and clinical experience in psychotherapy, licensed to practice independently, serving as the lead monitor. Examples of such professional credentials include the following:*

The ISCTM suggests that a distinction should be made between license and degree. For example, LCSW is the license in social work whereas MSW is the conferred degree. Additionally, the list of acceptable qualifications should be expanded, for example, to include a Nurse Practitioner or a Pharmacist. We therefore recommend that wording be amended as follows:

A healthcare provider with graduate-level professional training and clinical experience, licensed to practice independently, serving as the lead monitor. Examples of such professional credentials include, but are not limited to, the following:

Line 352 states, *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.*

Although useful to know the expected length of observation needed to characterize acute effects, the 12-week duration is not consistent with other indication-specific guidelines published by the FDA. The primary endpoint for the pivotal trials could be earlier based on the compound and indication; in that case the 12-week timepoint would be part of the durability assessment. The ISCTM requests the FDA to clarify whether indication-specific guidance will also apply or whether the psychedelics guidance will supersede those.