FDA's New Draft Guidance for Psychedelic Drugs Opens Doors for Drug Developers in the US

In July 2023, Australia became the first country to permit psychiatrists to prescribe 3,4-methylenedioxymethamphetamine (MDMA) and psilocybin for use in psychedelic-assisted psychotherapy to treat certain mental health conditions (MDMA for post-traumatic stress disorder [PTSD] and psilocybin for treatment-resistant depression [TRD]).[1] This change in regulation directly followed an action taken by the US Food and Drug Administration (FDA) that could accelerate similar changes in the US. It also came on the heels of positive published results from a clinical program evaluating MDMA as a treatment for PTSD that is close to seeking regulatory action.

In June 2023, the FDA published the draft guidance for industry, *Psychedelic Drugs: Considerations for Clinical Investigations*, to provide a resource for investigations of psychedelic drugs to treat specific medical conditions (eg, depression, PTSD, substance use disorders).[2] It is the first FDA guidance document created to aid industry in designing clinical trials for these products. In the agency's announcement[3] of the availability of the guidance, Tiffany Farchione, MD, director, Division of Psychiatry, Center for Drug Evaluation and Research, FDA, noted that "sponsors evaluating the therapeutic potential of these drugs should consider their unique characteristics when designing clinical studies" as they are "still investigational products." The guidance provides developers with information about clinical trial conduct, data collection, safety for trial participants, and requirements for new drug applications (NDAs).

The agency clarified in the guidance that the term "psychedelics" refers to "classic psychedelics," which are generally understood to be drugs such as psilocybin (a hallucinogenic chemical found in specific mushrooms) and lysergic acid diethylamide (LSD) that influence the brain's serotonin system, and "entactogens" or "empathogens" (eg, MDMA).

When conducting clinical studies for these agents, specific safety considerations include psychoactive effects (eg, mood and cognitive changes, hallucinations), which create an environment for abuse potential and require safety measures to prevent misuse throughout development. The FDA's 2017 guidance for industry, *Assessment of Abuse Potential of Drugs*,[4] provides information about how sponsors can assess the abuse potential of their drugs through study investigations of chemistry, pharmacology, pharmacokinetics, animal and human behaviour, abuse-related adverse events (AEs) in human studies, and abuse reports from other sources.

Investigations occurring under an investigational new drug application (IND) for products that the Drug Enforcement Administration (DEA) has classified as schedule I controlled substances under the Controlled Substances Act (CSA) must comply with applicable DEA regulatory requirements, the FDA noted. MDMA and psilocybin are both schedule I substances.

Potential Groundbreaking Regulatory Action

At the forefront of the psychedelic-drugs-as-therapeutics movement in the US is the Multidisciplinary Association for Psychedelic Studies (MAPS), which has been evaluating psychedelic-assisted psychotherapy since 1992. In 1985, the DEA criminalised the use and possession of MDMA; in response, MAPS was founded in 1986 to facilitate research and education about this treatment option. Several MAPS studies have evaluated the safety and effectiveness of MDMA-assisted psychotherapy for the treatment of PTSD, and the FDA granted MAPS breakthrough therapy designation to MDMA for this indication in 2017. Recent reports from MAPS suggest that MDMA could face a regulatory decision as early as 2024 after a planned submission of an NDA later in 2023.[5]

The most recent published data[6] supporting the safety and effectiveness of MAPS's MDMA-assisted psychotherapy to treat PTSD comes from a second, confirmatory phase III study completed in November 2022. The randomised, double-blind, placebo-controlled, multisite study (MAPP2) evaluated manualised MDMA-assisted psychotherapy (MDMA-AT) for the treatment of PTSD of moderate or greater severity in >100 participants aged ≥18 years. The primary endpoint was change from baseline in Clinician-Administered PTSD Scale for DSM 5 (CAPS-5), and the key secondary endpoint was change from baseline in Sheehan Disability Scale (adapted SDS) total score. Participants were randomised to receive a flexible dose of MDMA 80 or 120 mg or placebo, followed by a supplemental half-dose of 40 or 60 mg MDMA or placebo with manualised MDMA-assisted psychotherapy in 3 monthly experimental sessions.

In September 2023, MAPS announced publication of the MAPP2 study results.[7] The least squares (LS) mean change in CAPS-5 score (95% confidence interval [CI]) was -23.7 (-26.94, -20.44) for MDMA-AT versus -14.8 (-18.28, -11.28) for placebo with therapy (p-value = <0.001), demonstrating statistically significant improvement in PTSD after 3 sessions. The LS mean change in SDS score (95% CI) was 3.3 (-4.03, -2.60) for MDMA-AT versus -2.1 (-2.89, -1.33) for placebo with therapy (p-value = 0.03). In the MDMA-AT group, five participants had a severe treatment-emergent adverse event (TEAE) compared to two in the placebo group. There were no deaths or serious TEAEs in the study.

Overall, approximately 1,700 participants have received MDMA in the clinical program with only one serious adverse reaction. MAPS is also enrolling 400 participants by invitation for a long-term study (MPLONG) assessing the safety and effectiveness of MDMA-AT for PTSD, which began in March 2021 and is projected to complete in September 2024.

Additional Psychedelic Agents in Clinical Development

As of February 2023, COMP-360, a synthesised formulation of psilocybin developed by COMPASS Pathways plc that received breakthrough therapy designation by the FDA in 2018, has advanced to phase 3 as a candidate for TRD. A multicenter, randomized, double-blind, controlled study is recruiting >560 participants to investigate the efficacy, safety, and tolerability of two administrations of COMP360 administered with psychological support in adults with TRD. Participants are randomized 2:1:1 to receive COMP360 25 mg, 10 mg, or 1 mg. The primary outcome measure is the change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score at week 6. The study is estimated to complete in May 2025.

Usona Institute (Usona) is planning[8] a new study to evaluate the safety and efficacy of PSIL201, a chemically synthesized form of psilocybin, to treat major depressive disorder (MDD) after promising results from its randomised, double-blind, placebo-controlled phase 2 study evaluating a single oral dose of PSIL201, which was conducted in collaboration with The Emmes Company, LLC. Participants were randomised 1:1 to receive PSIL201 25 mg or oral niacin 100 mg, which served as an active placebo. In August 2023, Usona announced[9] the publication of results from the study, which showed that treatment with PSIL201 resulted in a mean difference of 12.3 (95% CI: -17.5, -7.2; p-value <0.001) from baseline to day 43. Compared with niacin, treatment with PSIL201 resulted in a mean difference of -2.31 (95% CI: 3.50, 1.11; p-value <0.001) in SDS scores from baseline to day 43. No serious TEAEs were reported, although participants who received PSIL201 had a higher rate of overall AEs and severe AEs.

The First Step

While US regulatory complications seem inevitable, the potential approval of a psychedelic in the next year presents an opportunity for much more research in this space and provides a novel approach to treating people with mental health conditions. The FDA will not regulate the psychotherapy element of the treatment; however, it will be possible to note the requirement in the labelling. The approval of a psychedelic as a medical treatment would signal the possibility of overcoming decades of legislative hurdles and the ever-present war on drugs to meet patients' needs, especially amid an ongoing acceptance of the medical and recreational use of cannabis in many US states – arguably the first battle the medical community fought to destigmatize scheduled substances.

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