November 20, 2026

Comment per Docket No. FDA-2026-N-10429

Re: Design and Safety Considerations for Clinical Trials Involving Ibogaine Drug Products; Request for Information.

To Whom It May Concern:

Ibogaine is one of several psychedelics (e.g., "magic mushrooms," LSD, "ecstasy," ketamine) that are newly being considered as bona fide medical treatments for major mental illness. The potential use of psychedelics to treat various forms of brain-based illness such as substance use disorders, post-traumatic stress disorder, and major depression is tied to "unmet need" and the acute psychological effects of psychedelics. As has been noted by many commentators, those effects are generally "profound and unpredictable," attributes that make it challenging to avoid functional unblinding in trials that compare a psychedelic to a placebo and make it difficult to avoid unintended effects.[1,2]

The mechanisms by which psychedelics are hypothesized to convey therapeutic benefit are speculative and concerning. A 2026 review by Siegel et al. published in *Nature Medicine* concluded that existing science points to a two-component neurobiological mechanism of psychedelic action.[3] First, these drugs are posited to "desynchronize" existing brain signals and networks. Second, psychedelics create a time-limited window for presumed therapeutic neuroplasticity (nerve network remodeling/rewiring). As compelling as these theories may be, empirical data supporting them are only now emerging and mixed.

For example, a 2026 study conducted in adult mice showed that disruption of binocular visual pathways (by sewing one eye shut) responds to ibogaine treatment by pruning nerve connections in the deprived eye.[4] Although this work suggests that ibogaine reverted the stimuli-deprived connections in the brain to a "youthful, juvenile" status, these results did not show a parallel bolstering of the contralateral visual pathway. Accordingly, an alternative interpretation of this result is that ibogaine accelerates the dismantling of

[1] Food and Drug Administration. Considerations for potential future therapeutic use of psychedelic drugs public hearing. September 14, 2026. https://www.youtube.com/live/5Kg1gj3KbAI. Accessed November 18, 2026.
[2] Food and Drug Administration. Psychedelic drugs: considerations for clinical investigations. Guidance for industry. July 2026. https://www.fda.gov/media/169694/download. Accessed November 19, 2026.
[3] Siegel JS, Liston C, Nicol GE, et al. The science of psychedelic medicine. *Nat Med*. 2026 Feb;32(2):449-462.
[4] Acuña A, Billeri F, Totaro V, et al. Ibogaine induces juvenile-like plasticity and modulates functional and structural regulators of plasticity in the adult mouse visual cortex. *BMC Neurosci*. 2026 May 13;27(1):39.

certain unused circuits without necessarily preparing other circuits for recovery and adaptation.

Separately, a recent study in zebrafish showed that ibogaine administration disrupts or alters developing nervous and other organ systems.[5] Specifically, zebrafish embryos exposed to ibogaine experienced, or developed into larvae with, signs of cardiac impairment and hyperactivity at higher rates than unexposed embryos. Zebrafish are a convenient, long-established model for general nervous and other organ system development because they mature rapidly and their young somas are transparent for easy morphologic review.

These recent preclinical studies illustrate what is currently known about the power and potential toxic effects of ibogaine on the nervous system and more generally. Mouse and lower-phylum models can assess organ and behavioral changes to consider if the linchpin theory of psychedelic-induced neuroplasticity is plausible for a given drug, illusory or worse (i.e., more injurious than beneficial). Because ibogaine's safety and mechanistic effectiveness remain uncertain, the FDA should require more preclinical studies as the foundation for any future human testing.

With mounting pressure to develop psychedelic remedies, including ibogaine, the FDA should also follow its highest premarket-gatekeeping principles, many of which were outlined in the agency's July 2026 guidance-to-industry document entitled "Psychedelic drugs: considerations for clinical investigations."[6]

Clinical trials submitted to the FDA for a new drug application (NDA), especially involving a psychedelic such as ibogaine, should address the problems of functional unblinding (stemming from the intense "mind-altering" effects of the active drug) and research participants' expectation bias (an *a priori* belief that a certain result will occur). The FDA guidance offers sponsors limited suggestions on how to cope with these critical concerns, such as varying-dose or alternative psychoactive drug comparison arms, and empirical assessment of unblinding and bias throughout the duration of the trial. The FDA should further disseminate and mandate more specific unblinding and bias-mitigating methods such as the following:

1. Requiring sponsors to enroll a full and balanced spectrum of psychedelic-hesitant to psychedelic-eager participants in their pivotal studies and use a standardized measure of that expectation as a covariate in outcomes analyses. Involving psychedelic-skeptical therapists may also be useful.

2. Requiring sponsors to create comparison interventions that have sufficient salience to compete with the intensive "mind-altering" effects of psychedelics. For example,

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[5] de Oliveira AL, Abe FR, Dos Santos RG, et al. Ibogaine as a double-edged sword: Developmental cardiotoxicity and neurobehavioral alterations in zebrafish. *Behav Brain Res*. 2026 Oct 18;515:116429.
[6] Food and Drug Administration. Psychedelic drugs: considerations for clinical investigations. Guidance for industry. July 2026. https://www.fda.gov/media/169694/download. Accessed November 19, 2026.

novel and exciting behavioral approaches (e.g., the introduction of pleasing physical exercise or other stimuli) could be compared with a psychedelic exposure to confirm or refute the hypothesis that a drug is distinctly cathartic.

3. Maintaining a public list that details psychoactive drugs that might serve as reasonable comparators.

The FDA also should require that psychedelic-NDA sponsors submit applications that fully detail and measure the independent effects of the intensive support sessions that are typically used for psychedelic drug administration and follow-up. Those support sessions often require hours-long oversight and psychotherapy delivered by multiple, trained facilitators. At present, the FDA guidance says only that it "may be useful" to design trials that can discern the independent effects of these supportive services. The FDA should require that trials are designed to evaluate the independent effects of supportive services and commit to having sufficient psychotherapy experts as agency employees or contractors to evaluate such multimodality treatment protocols.

Finally, the FDA should require that trials of ibogaine quantify the potential of cardiovascular and addiction risks (among others), including assessing euphoria-inducing effects, even if such effects may sometimes be perceived as therapeutic or otherwise desirable.

Public Citizen appreciates the opportunity to comment on these important issues.

Respectfully submitted,

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