field trip

February 14, 2022

Drug Enforcement Administration
Attn: DEA FR Representative/DPW
8701 Morrissette Drive
Springfield, Virginia 22152

RE: Docket No. DEA-623
Schedules of Controlled Substances: Placement of 4-hydroxy-N,N-diisopropyltryptamine, 5-methoxy-alpha-methyltryptamine, 5-methoxy-N-methyl-N-isopropyltryptamine, 5-methoxy-N,N-diethyltryptamine, and N,N-diisopropyltryptamine in Schedule I
CONTAINS CONFIDENTIAL BUSINESS INFORMATION

Dear Sir/Madam:

This submission is made by Field Trip Discovery USA Inc. ("Field Trip Discovery"), a research-based, data-driven biopharmaceutical company pursuing development and ultimately regulatory approval for pioneering, short-acting, physician-administered medicinal products that hold the potential to address a range of significant unmet medical needs across multiple patient populations struggling with a range of psychiatric and neurological diseases. Field Trip Discovery is pleased to submit its comments to the Drug Enforcement Administration ("DEA") on its Notice of Proposed Rulemaking for Schedules of Controlled Substances published in the Federal Register on January 14, 2022 (87 Fed. Reg. 2376). This submission **CONTAINS CONFIDENTIAL BUSINESS INFORMATION ("CBI") that is marked for redaction by bolded brackets with CBI text highlighted in blue as follows: [CBI]**.

Field Trip Discovery appreciates DEA's ongoing efforts to prevent the diversion and abuse of controlled substances and concurs with the DEA's proposal to place into Schedule I of the CSA the latter four (4) compounds which are identified in the subject heading of this rulemaking. As detailed more fully in this submission, Field Trip Discovery does not believe that scheduling of *4-hydroxy-N,N-diisopropyltryptamine* ("4-OH-DiPT") is justified or warranted at this time based either on the legacy 10-year-old data relied upon by the DEA in this rulemaking or by any other data or information suggesting that 4-OH-DiPT is properly classified a substance of abuse. The new and more current data and information presented in this submission reflects that it is not a substance of abuse. In addition, the DEA's proposal to place 4-OH-DiPT in Schedule I of the Controlled Substances Act ("CSA") would significantly adversely affect the ongoing research and development ("R&D") on [ ] Field Trip Discovery's lead investigational drug candidate, FT-104 [ ].

FT-104 is a [redacted]. As has been well-documented in other contexts, the barriers to research imposed by Schedule I regulation are formidable, and, while the effect is not an outright ban on such research, the practical consequence has been to stifle research on potential therapeutic compounds placed in Schedule I. For all of the reasons set forth below, Field Trip Discovery believes it is imperative to avoid such barriers to the ongoing R&D of FT-104 given that the significant potential therapeutic benefits of FT-104 are very real and of potential medical and public health significance.

Because the new and extensive drug development data and information presented in and appended to this submission was not available to the DEA and was not part of the administrative record considered by the DEA when it promulgated this notice of proposed rulemaking, Field Trip Discovery respectfully requests that the DEA defer any scheduling of 4-OH-DiPT until the completion of the FT-104 development program. Upon successful development of FT-104, FDA will complete the standard 8-factor CSA analysis based upon data submitted by Field Trip Discovery [redacted]. Deferring any scheduling of 4-OH-DiPT will enable Field Trip Discovery's development program to advance into and complete its development, [redacted].

As reflected in the comprehensive analysis in the ensuing sections of this submission, the administrative record upon which DEA relied in promulgating this notice of proposed rulemaking is woefully inadequate, outdated, and incomplete to support placement of 4-OH-DiPT in Schedule I of the CSA. Relying on a ten (10)-year-old report and taking some perfunctory step to "confirm" that the statements in it "are still applicable" is not a rational or reasonable basis upon which to initiate this or any other administrative action, especially given

---

1 [redacted].

the gravity of this rulemaking's consequences. Accordingly, as a matter of sound science and administrative law, evaluation of the entire administrative record – which now includes the extensive new data in this submission and its appendices – makes it apparent that deferring scheduling of 4-OH-DiPT is the appropriate administrative action for the DEA at this juncture. (*See also* footnote 1).

Scientific Background On FT-104

The drug substance [redacted] of 4-OH-DiPT. Following extensive drug-discovery research and development ("R&D"), Field Trip Discovery selected this [redacted] of 4-OH-DiPT for development for use in the treatment of significant mental disorders, including [redacted].

FT-104 is being developed as a [redacted].

[redacted], 4-OH-DiPT, acts as a serotonin (5HT) agonist, notably on 5-HT_{2a} and 5-HT_{2b} subtypes, and these receptors have been suggested to contribute to 4-OH-DiPT-mediated activity. 4-OH-DiPT is a 4-hydroxytryptamine and a serotonin agonist, which has structural and pharmacological similarities to psilocybin, which has received breakthrough therapy designation ("BTD") by

---

2 [redacted].

FDA for the treatment of major depressive disorder.[3] Agonist activity at the serotonin-2A ($5HT_{2A}$) receptor is believed to be the primary mechanism of the antidepressant effects seen in animal models and in human clinical studies of psilocybin.

There is an emerging body of peer-reviewed data that were not considered by the DEA in this rulemaking reflecting that 4-OH-DiPT has a remarkably different receptor profile directed at neural plasticity. This distinct receptor profile stands in stark contrast to the other four compounds that are the subject of this rulemaking and similar hallucinogenic street drugs of abuse. It is because of this novel receptor profile that FT-104 holds such therapeutic potential. Indeed, several lines of evidence suggest that such serotonergic compounds have clinical potential for inducing therapeutically-beneficial behavior changes in a variety of psychiatric conditions.

A peer-reviewed study published in 2016 (Rickli et al., European Neuropsychopharmacology (2016) 26:1327-37)[4] includes new data on 4-OH-DiPT showing that "it is a 5-HT_{2A} receptor partial agonist[], a SERT inhibitor[], and a weak NET inhibitor[], exhibiting a similar profile to psilocin," the pharmacologically active molecule into which psilocybin is converted in the liver. (*See* footnote 3, above.) The results in that study "indicate that activity at the SERT may contribute to the pharmacology" of 4-OH-DiPT, because its "SERT inhibition potency is in the range of the binding potency at the 5-HT_{2A} receptor." (Ibid.). Moreover, unlike each of the other compounds that are the subject of this rulemaking, the effects

---

[3] Although somewhat beyond the scope of this rulemaking, it nonetheless is noteworthy in this context (given the structural relationship between 4-OH-DiPT and psilocin) that several studies with psilocybin have shown promising and long lasting results, *e.g.*, in a study in cancer patients with anxiety and/or mood symptoms (Griffiths et al., J. Psychopharmacol. (2016), 30(12):1181-1197), (Ross et al., J. Psychopharmacol. (2016), 30(12) 1165-1180), and a study in patients with treatment resistant depression (Carhart-Harris, Lancet Psychiatry (2016), 3(7):619-627), (Carhart-Harris, N Engl J Med (2021), 384(15):1402-1411). Promising results also were obtained in a study in patients with an obsessive-compulsive disorder (Moreno et al,, J. Clin Psychiatry (2006), 67(11):1735-1740), and alcohol (Bogenschutz et al., J. Psychopharmacol. (2015), 29(3):289-299), and tobacco dependency (Johnson et al., J. Psychopharmacol. (2014), 28(11):983-992). Additionally, controlled trials that included subjects with mood disorders have demonstrated acute and long-term (6 months) improvement in mood and anxiety symptoms in patients with advanced-stage cancer. (Ross et al., J Psychopharmacol. (2016), 30(12):1165-1180), (Grob et al., Arch Gen Psychiatry (2011), 68(1):71-78), (Griffiths et al., J Psychopharmacol. (2016), 30(12):1181-1197). The most recent study, which was published last year (April 15, 2021 edition) in the New England Journal Of Medicine, found that psilocybin was equivalent to 14 days therapy with escitalopram in treating patients suffering from moderate-to-severe major depressive disorder. (Carhart-Harris et al., N Engl J Med (2021), 384:1402-1411). None of these studies cited in this footnote 3 or the data they present were in the administrative record considered by the DEA or addressed in the DEA's Notice of Proposed Rulemaking.

[4] This study and the data it presents were not in the administrative record considered by the DEA or addressed in the DEA's Notice of Proposed Rulemaking.

of 4-OH-DiPT are distinguished by their relative brevity. Indeed, a study published in 2015 (Tittarelli et al., Current Neuropharmacology (2015) 13:26-46)[5] found that, even with oral administration, the 4-OH-DiPT duration of action was uniquely brief. [redacted].

Enduring changes in attitudes, depression, anxiety, wellbeing, substance misuse, and mindfulness have been documented after administration of serotonergic compounds. Connectedness, emotional breakthrough, and increased neural entropy are related to these long-term changes in psychological functioning. (Aday et al., Neurosci Biobehav Rev (2019), 113:179-189).[6] Additionally, there is emerging evidence that serotonergic-assisted psychotherapy can be a potent treatment for depression and other psychological disorders. (Carhart-Harris et al., Lancet Psychiatry, (2016), 3(7):619-627).[7] Serotonin-2a agonists are reported to inhibit the default mode network in the brain, a regulating portion of the neural structure, thus allowing a greater interaction of other neural networks and the potential for personal introspection, greater insights into depression origins, behaviors, and triggers. Serotonin agonists also can promote increased neural plasticity in areas of the prefrontal cortex, and this is believed to underlie the antidepressant effects of these agents. Indeed, recent study results" provide direct evidence" that such medicinal products can "promote structural and functional neural plasticity" and thus "underscore the therapeutic potential" of serotonergic compounds and support "medicinal chemistry efforts focused on developing plasticity-promoting compounds as safe, effective, and fast-acting treatments for depression and related disorders." (Ly et al., Cell Rep. (2018), 23(11):3170-3182).[8] [redacted].

Although no formal human studies with 4-OH-DiPT have been recorded to the knowledge of Field Trip Discovery, the literature does present limited pharmacological and non-clinical studies. A very recent review manuscript on serotonergic compounds (Andersen et al.,

---

[5] This study and the data it presents were not in the administrative record considered by the DEA or addressed in the DEA's Notice of Proposed Rulemaking.

[6] This study and the data it presents were not in the administrative record considered by the DEA or addressed in the DEA's Notice of Proposed Rulemaking.

[7] This study and the data it presents were not in the administrative record considered by the DEA or addressed in the DEA's Notice of Proposed Rulemaking.

[8] This study and the data it presents were not in the administrative record considered by the DEA or addressed in the DEA's Notice of Proposed Rulemaking.

Acta Psychiatr Scand., 143 (2), 101-118, 2021)[9] concluded that there is evidence for treatment efficacy and safety for a range of psychiatric conditions. Controlled studies on the safety, tolerability, and pharmacokinetics of 4-OH-DiPT in human, however, are lacking. However, importantly in the context of this submission, Field Trip Discovery [redacted] and is preparing to initiate its [redacted].

[redacted]. Importantly, however, receptor binding studies (5-HT_{2a} and 5-HT_{2b} agonist radioligand assays) have indicated that 4-OH-DiPT administered as such is more potent than [redacted]. Serotonin receptor activation can occur through direct and indirect methods, by direct agonist activation or indirectly by increasing extracellular serotonin in the synapses.

[redacted].

[redacted].

[redacted]

[9] This study and the data it presents were not in the administrative record considered by the DEA or addressed in the DEA's Notice of Proposed Rulemaking.

[redacted].

[redacted]

[redacted].

[redacted].

The Absence Of Abuse Potential For 4-OH-DiPT Warrants Deferring Scheduling At This Time

The FDA is the focal point for abuse potential assessments, and FDA works with an NDA sponsor to determine the range of studies needed to enable FDA's review and evaluation of the NDA in order to determine approvability, any scheduling recommendation, and all aspects of labeling (portions of which are based on the abuse potential assessment and scheduling). The submission required by FDA for an abuse potential assessment is comprised of five separate modules, which include the sponsor's scheduling proposal and rationale in Module 1, and a summary and thorough discussion of all abuse related nonclinical and clinical data in Module 2. Modules 3, 4, and 5 include complete study protocols and data addressing chemistry, in vitro and non-human pharmacology, and clinical studies including the integrated summary of safety (ISS), respectively. As any sponsor would do, Field Trip Discovery intends to complete all of these for FDA's review and evaluation.

Even at this stage of development, however, it is apparent that an assessment of all eight factors that guide the FDA and DEA recommendations for CSA scheduling do not currently support scheduling of 4-OH-DiPT. Field Trip Discovery believes that the proposal in this notice of proposed rulemaking to place 4-OH-DiPT in Schedule I resulted from outdated legacy data that led to a substantial overestimation of the risk of harm and abuse potential. The CSA stipulates that Schedule I is for substances with a high potential for abuse, lack of therapeutic approval, and that cannot be used safely in medicine. The available new scientific data presented in this submission (which were not before the DEA when it initiated this rulemaking) concretely demonstrate that the first and third criteria simply do not apply, and that, as to the second criterion, the significant potential therapeutic benefits of FT-104 are very real and of potential medical and public health significance. Accordingly, taking into account the data presented in the preceding section and in the considerations addressed below, it is apparent that 4-OH-DiPT should not be placed in Schedule I of the CSA.

First, there are no data demonstrating that individuals are administering quantities of 4-OH-DiPT sufficient to create a hazard to their health or to the safety of other individuals or to the community. Indeed, among the various legacy data cited by the DEA in its Proposed Rule from 2012 and earlier, there are no human cases of addiction cited, and Field Trip Discovery is unaware of any reports of human addiction to 4-OH-DiPT.

Second, although abuse of 5-MeO-AMT and 5-MeO-MiPT has been associated with hospital emergency room admissions, there are no data of which Field Trip Discovery is aware of hospital emergency room admissions involving 4-OH-DiPT.

Third, as the DEA itself acknowledged in this rulemaking, 4-OH-DiPT is available for purchase from legitimate chemical companies because they are used in scientific research. No evidence of diversion is apparent from these companies.

Fourth, as to FT-104 itself, even if it were somehow to be diverted during Field Trip Discovery's development program (which is not a reasonable prospect), it is highly unlikely that individuals would administer FT-104 on their own initiative since [redacted]. Additionally, [redacted]. Thus, there is little to no practical risk to public health from drug product abuse.

Fifth, to Field Trip Discovery's knowledge, there have been no reports of abuse of 4-OH-DiPT, and there have been no reports of drug seizures of which Field Trip Discovery is aware since the legacy data cited in the DEA's rulemaking.

Sixth, the available evidence suggests that there is no psychic or physiological dependence potential of FDA-regulated products containing 4-OH-DiPT. The psychic or physiological dependence potential of FDA-regulated products is currently expected to be very limited due to the aforementioned low potential for abuse and the extremely high and lethal quantities needed to achieve a subjective "high."

Seventh, 4-OH-DiPT is not an immediate precursor of a substance already controlled under the CSA.

Eighth, 4-OH-DiPT will not have any significant capability of creating hazards to the health of patients administered FT-104 or to the safety of the community, as it is designed as a

physician-administered medication and therefore use would be restrained to clinicians, with controlled substance licenses and trained to administer the medication in accordance with the [redacted].

* * *

Based upon the foregoing scientific and medical evaluation, and based on the DEA's consideration of all the extensive new data and information presented in this submission and its appendices, it is apparent that the entire administrative record demonstrates that 4-OH-DiPT does not possess abuse or dependence potential. Accordingly, the DEA should find that the facts and all available and relevant data amply support the conclusion that 4-OH-DiPT does not meet the requirements for inclusion in any schedule and that scheduling of 4-OH-DiPT is not warranted. Accordingly, Field Trip Discovery requests that the DEA withdraw 4-OH-DiPT from this rulemaking and defer any scheduling of it at this time.

In the meantime, if there are any questions on this submission or if any additional information is required in connection with it, please contact the undersigned by phone at 1-416-388-5725 or by email at nathan@fieldtriphealth.com.

Thank you in advance for your time and consideration.

Respectfully submitted,

_____
Nathan Bryson, Ph.D.
Chief Scientific Officer
Field Trip Discovery USA Inc.

Enclosures: Reference List Of Published Studies Attached Separately
Full Texts Of Published Studies Cited On The Reference List

Reference List Of Published Studies Attached Separately
(In Alphabetical Order By Lead Author Last Name)

J.S. Aday, C.M. Mitzkovitz, E.K. Bloesch, C.C. Davoli, A.K. Davis, Long-term effects of psychedelic drugs: A systematic review. Neurosci Biobehav Rev, 113:179-189, 2019.

K.A.A. Andersen, R. Carhart-Harris, D.J. Nutt and D. Erritzoe, Therapeutic effects of classic serotonergic psychedelics: a systematic review of modern-era clinical studies, Acta Psychiatr Scand, 143 (2), 101-118, 2021.

M.P. Bogenschutz, A.A. Forcehimes, J.A. Pommy, C.E. Wilcox, P.C. Barbosa and R.J. Strassman, Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study, J. Psychopharmacol, 29(3), 289-299, 2015.

R.L. Carhart-Harris, B. Giribaldi, R. Watts, M. Baker-Jones, A. Murphy-Beiner, R. Murphy, J. Martell, A. Blemings, D. Erritzoe and D.J. Nutt, Trial of psilocybin versus escitalopram for depression, New England Journal of Medicine, 384(15), 1402-1411, 2021.

R.L. Carhart-Harris, M. Bolstridge, J. Rucker, C.M. Day, D. Erritzoe, M. Kaelen, M. Bloomfield, J.A. Rickard, B. Forbes, A. Feilding, D. Taylor, S. Pilling, V.H. Curran and D.J. Nutt, Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study, Lancet Psychiatry, 3(7), 619-627, 2016.

R.R. Griffiths, M.W. Johnson, M.A. Carducci, A. Umbricht, W.A. Richards, B.D. Richards, M.P. Cosimano and M.A. Klinedinst, Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. J. Psychopharmacol. 30(12), 1181-1197, 2016.

C.S. Grob, A.L. Danforth, G.S. Chopra, M. Hagerty, C.R. McKay, A.L. Halberstadt, G.R. Greer, Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer, Arch Gen Psychiatry, 68(1), 71-78, 2011.

M.W. Johnson, A. Garcia-Romeu, M.P. Cosimano and R.F. Griffith, Pilot study of the 5-HT2aR agonist psilocybin in the treatment of tobacco addiction, J. Psychopharmacol, 28(11), 983-992, 2014.

C. Ly, A.C. Greb, L.P. Cameron, J.M. Wong , E.V. Barragan, P.C. Wilson, K.F. Burbach , S.S. Zarandi, A. Sood, M.R. Paddy, W.C. Duim, M.Y. Dennis, A.K. McAllister , K.M. Ori-McKenney, J.A. Gray, D.E. Olson, Psychedelics Promote Structural and Functional Neural Plasticity, Cell Rep, 12;23(11), 3170-3182, 2018.

F.A. Moreno, C.B. Wiegand, E.K. Taitano and P.L. Delgado, Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder, J. Clin Psychiatry, 67(11), 1735-1740, 2006.

A, Rickli, O.D. Moning, M.C. Hoener, and M.E. Liechti, Receptor interaction profiles of novel psychoactive tryptamines compared with classic hallucinogens, European Neuropsychopharmacology, 26, 1327-1337, 2016.

Ross, A. Bossis, J. Guss, G. Agin-Liebes, T. Malone, B. Cohen, S.E. Mennenga, A. Belser, K. Kalliontzi, J. Babb, Z. Su, P. Corby, and B.L. Schmidt, Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression I patients with life-threatening cancer: a randomized controlled trial, J. Psychopharmacol, 30(12), 1165-1180, 2016.

R. Tittarelli, G. Mannocchi, F. Pantano, and F.S. Romolo, Recreational Use, Analysis and Toxicity of Tryptamines, Current Neuropharmacology, 13, 26-46, 2015.