February 10, 2022

Drug Enforcement Administration
Attn: Hearing Clerk/OALJ
8701 Morrissette Drive
Springfield, VA 22152

Re: *Docket No. DEA-623*

Dear Sir:

Petitioners[1] hereby request a hearing in the matter of: *Schedules of Controlled Substances: Placement of 4-hydroxy*-N,N-*diisopropyltryptamine (4-OH-DiPT), 5-methoxy*-alpha-*methyltryptamine (5-MeO-AMT), 5-methoxy*-N-*methyl*-N-*isopropyltryptamine (5-MeO-MiPT), 5-methoxy*-N,N-*diethyltryptamine (5-MeO-DET), and* N,N-*diisopropyltryptamine (DiPT) in Schedule I.*

Introduction

DEA recently published in the Federal Register a notice of proposed rulemaking proposing to place Five Tryptamine[2] hallucinogens into Schedule I. 87 Fed. Reg. 2376 (Jan. 14, 2022) (the "proposed rule"). Based on an HHS evaluation from 2012, DEA concludes that these compounds meet the criteria for placement in Schedule I.

Petitioners oppose the rule as proposed. The evidence of actual or potential abuse presented in the proposed rule and supporting materials does not justify placement of one or more of the Five Tryptamines into Schedule I. Placing these substances in Schedule I would greatly disturb ongoing research into these Five Tryptamines and other related compounds—research that could transform mental health care at a moment in time when new treatments are desperately needed.

Petitioners encourage DEA to withdraw or delay the proposed rule and continue to regulate the Five Tryptamines under the Federal Analogue Act. Alternatively, if DEA concludes that the law and evidence warrants control of the Five Tryptamines, Petitioners urge DEA to consider alternative placements, such as Schedules II or III.

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1 Mindstate Design Labs (Kykeon Biotechnologies Inc.) and Tactogen Inc.

2 4-OH-DiPT, 5-MeO-AMT, 5-MeO-MiPT, 5-MeO-DET, and DiPT.

Comment/Request for Hearing

(A) Statements of Interest

- **Mindstate Design Labs** (Kykeon Biotechnologies Inc.) is a Pennsylvania-based company that develops psychedelic drug therapies for intractable mental health conditions. It is currently investigating one or more of the Five Tryptamines in preclinical research. Its website is at https://www.mindstate.design/.

- **Tactogen Inc** is a California-based public benefit corporation that is developing safer, more effective prescription medicines for mental wellness. It is currently investigating one or more of the Five Tryptamines as part of a program to develop new medicines. Its website is at https://tactogen.com/.

(B) Objections/Issues[3]

1. Whether the proposed rule's reliance on the 2012 HHS evaluation is arbitrary, capricious, or contrary to law; whether DEA failed to observe the procedure required by the CSA; and whether the HHS analyses must be updated before DEA can institute rulemaking.

2. Whether significant aspects of the § 811(b) analyses are arbitrary, capricious, contrary to law, or lack substantial evidence.

3. Whether the proposed rule sets forth subsantial evidence to support actual or potential for abuse.

4. Whether a finding that a substance lacks accepted medical use is dispositive of a classification.

5. Whether DEA complied with the Regulatory Flexibility Act; and whether it must conduct an initial and final regulatory flexibility analysis.

(C) Statement of Positions on Objections/Issues

1. Use of a 2012 HHS Evaluation and Recommendation is Improper.

Scheduling evaluations by HHS and DEA must be based on *current* data. *See, e.g.*, 21 U.S.C. § 811(c)(4) ("history and *current* pattern of abuse"). Because the proposed rule relies on a 2012 HHS evaluation, however, it cannot be based on current data.

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[3] Petitioners request a hearing according to the rulemaking procedures prescribed by subchapter II of chapter 5 of title 5, but do not necessarily require a hearing on all six issues. Consistent with 21 C.F.R. § 1308.42, a hearing is only needed for the purpose of receiving factual evidence and expert opinion regarding the issues involved in the issuance of the rule. Other issues can be addressed in pre-hearing or post-hearing submissions.

After receiving the HHS evaluation, Section 811(b) states that "[i]f the Attorney General determines that these facts and all other relevant data constitute substantial evidence of potential for abuse such as to warrant control … he *shall* initiate proceedings for control." Here, DEA received the HHS evaluations in 2012. But DEA did not initiate proceedings shortly thereafter. Presumably, it concluded that the facts and relevant data did not constitute substantial evidence of potential for abuse to warrant control. The proposed rule provides no explanation for why, ten years later, DEA changed its mind.

DEA states that in June 2020, it "confirmed with HHS that their 2012 statements are still applicable," but only with respect to medical use. DEA does not explain why it did not ask HHS to update its 2012 evaluation. That is significant considering (1) the 2012 HHS evaluations rely on older research to generalize about hallucinogenic compounds, and (2) a wave of newer research calls into question older research and assumptions about the actual and potential abuse and risks of hallucinogenic compounds. A PubMed search for "hallucinogen" shows that the research surrounding hallucinogens has grown considerably since 2012, including 1,036 papers in 2020.

Indeed, DEA's eight-factor analysis relies on substantial relevant scientific research that post-dates the HHS evaluation, such as Rickli et al., 2016 and Janowsky, 2018a-f.[4] HHS in 2012 did not and could not consider this evidence. Some contradicts or undermines conclusions reached by HHS in its 2012 evaluations. For example, DEA states that drug discrimination studies in rats show that DiPT fully substitutes for DMT (citing Gatch and Forster, 2006d). But Carbonaro et al., 2015 and Carbonaro et al., 2013 explain that while DMT and DiPT are structurally similar hallucinogens, they produce different effects from each other and do not fully cross-substitute for each other. Excluding the HHS evaluations themselves, nearly 1 out of 3 references cited in DEA's analysis post-dates the 2012 HHS evaluation—none of which could have been considered by HHS in its 2012 review.

Section 811(b) requires DEA to request from the Secretary a scientific and medical evaluation "*after* gathering the necessary data." Therefore, DEA must ask HHS for a new or updated evaluation *before* initiating proceedings for control.

2. The Eight Factor § 811(b) Analysis is Fundamentally Flawed.

Several components of the eight-factor § 811(b) analysis are arbitrary, capricious, contrary to law, or lack substantial evidence. The following illustrates some of the deficiencies:

Factor 1(d) should not apply. None of the Five Tryptamines are *new* drugs. In its analysis, HHS states that it relied on the legislative history's definition. But the legislative history explains

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[4] Similarly, it is unclear why the DEA's analysis does not cite Gatch, Michael B et al. "Discriminative Stimulus Effects of Substituted Tryptamines in Rats." *ACS pharmacology & translational science* vol. 4,2 467-471. 29 Dec. 2020, which was research supported by contract 15DDHQ18P00000735 from HHS/DEA and appears to have been awarded prior to August 2019. Gatch et al., 2020 raises further questions about why DEA did not ask HHS for a current medical evaluation as the statute requires.

that the fourth "potential for abuse" factor applies to *new* drugs.[5] The Five Tryptamines, in contrast, have been around for decades. DEA's August 2021 § 811(b) analysis correctly restates the legislative history, but incorporates the flawed HHS analysis. And where, as here, the drugs are not *new*, it is not reasonable to make assumptions flatly contradicted by the available evidence.

Improper generalizations and conclusions. The § 811(b) analyses repeateadly make improper conclusions about the Five Tryptamines, tryptamines, and hallucinogens generally based on unsubstantiated statements and unsound scientific reasoning; for example:

- For factor 6, HHS concludes that "hallucinogen abusers may develop psychological dependence, as evidenced by continued use despite knowledge of potential toxic and adverse effects of the substances." This statement is unsubstantiated. Most hallucinogens are not "habit forming."[6] Hallucinogens are not typically considered to be drugs of dependence. Neither are they reliably self-administered in nonhuman animals, nor associated with a known withdrawal syndrome.[7]

- It is unclear how or why HHS selected certain hallucinogens (DOM, DMT, LSD, and mescaline) as comparators to the Five Tryptamines but not others. Neither DOM nor mescaline are tryptamines, for example. Research since 2012 has shown that the subjective effects of 4-substituted tryptamines such as 4-HO-MiPT are most closely related to psilocybin and its active metabolite psilocin.[8] The agencies should thus consider the detailed eight-factor analysis in light of Johnson, Matthew W et al. "The abuse potential of medical psilocybin according to the 8 factors of the Controlled Substances Act." *Neuropharmacology* vol. 142 (2018).

- For factor 5, DEA's eight-factor analysis states that "[t]ryptamine hallucinogens, both natural and synthetic, have been popular among the attendees of rave parties, music concerts, … Often these substances are promoted as substitutes for LSD. Synthetic hallucinogens and stimulants are known as 'club drugs.'" Moreover, DEA states that there "has been significant availability, trafficking, and abuse of a number of tryptamines." Generalizations aside, there is little evidence about the Five Tryptamines, for example, that any has ever been regarded as a "club drug."

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5 *See* H.R. Rep. No. 91-1444 91st. Cong., 2d Sess. 47 (1970) (House Report) at 34.

6 *See* House Report at 36 (explaining that "psychic or physiological dependence liability" requires an assessment of the extent to which a drug is "physically addictive or psychologically habit forming").

7 Johnson, Mw et al. "Human hallucinogen research: guidelines for safety." *Journal of psychopharmacology* (Oxford, England) vol. 22,6 (2008): 603-20.

8 Rickli, Anna et al. "Receptor interaction profiles of novel psychoactive tryptamines compared with classic hallucinogens." *European neuropsychopharmacology* vol. 26,8 (2016): 1327-37.

- That two substances may have similar molecular structure or may exhibit affinity over the same receptor is not a sufficient scientific basis to conclude that the two substances exhibit similar pharmacological action. For example, DEA states that "[c]hemically, 5-MeO-MiPT is a synthetic analogue of tryptamine, which is structurally related to other tryptamines, such as DMT. The effects and pharmacological action of 5-MeO-MiPT are therefore similar to that of other Schedule I hallucinogens, such as DMT or LSD, both of which have no accepted medical use and high abuse potential." This syllogism is not sound. For example, analogues of tryptamine include the prescription anti-migraine drug sumatriptan as well as the over-the-counter sleep aid melatonin.

Insufficient and Contrary Evidence. Numerous points and statements in the eight-factor analyses lack sufficient evidence, including but not limited to:

- In factors 1(a) and 6 in the HHS analysis of 5-MeO-MiPT, HHS concludes that individuals are taking 5-MeO-MiPT in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community based on *two* case reports in which a *combination* alleged to be 5-MeO-MiPT and harmala extracts/harmaline were consumed.[9] In one of the two cases, the evaluation notes that it is "unclear from the available information whether 5-MeO-MiPT played a direct role in the death." HHS also notes that there are "23 anecdotal case reports described on the Internet www.erowid.org in which individuals who purported to use 5-MeO-MiPT were treated by medical professionals," but it is unclear which reports on www.erowid.org HHS refers to. Many involve combinations of 5-MeO-MiPT and other substances.

- The HHS evaluation concludes that "[u]se of 5-MeO-MiPT is associated with emergency room admissions." It is unclear what evidence supports an association.

- The HHS evaluation concludes that evidence from law enforcement databases and case reports regarding seizures demonstrate that 4-OH-DiPT has been available as a "street drug" of abuse. But DEA's NFLIS database for drug cases did not report *any* cases involving 4-OH-DiPT, and only *three* cases reported in DEA's STRIDE database from 2003 to 2004. None of those three cases provide evidence to support any scope, duration, or significance of abuse and do not support the conclusion that 4-OH-DiPT's has been available for purchase as a street drug. The conclusion runs "counter to the evidence before the agency." *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).

Methodology and Standards Used. In making § 811(b) determinations and assessing the research, it is unclear what standards DEA and HHS apply to the evidence. For many items, a handful anecdotal reports reported over a period of years is deemed sufficient in support of abuse

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[9] That a combination of an MAOI and 5-MeO-MiPT may have led to a hospital admission and death says little about whether 5-MeO-MiPT itself is sufficient to create a hazard. The proposed rule does not present evidence suggesting a pattern of combining of these substances.

potential. In contrast, in July 2016, in responding to a petition to reschedule marijuana by the Governors of Washington and Rhode Island, HHS did a searching review of publicly available medical literature; determined that only 11 out of 566 studies met the selection criteria, including placebo and double-blinding; and critically reviewed those 11 studies, concluding that none proved efficacy due to "limitations in the study designs."[10] In short, the agencies appear to be applying wildly different standards in different scheduling actions. This unexplained inconsistency and departure from prior practice renders the proposed rule arbitrary and capricious. *See Encino Motorcars, LLC v. Navarro*, 579 U.S. 211, 221 (2016).

Risk to Public Health. The eight-factor analysis presumes that any drug that induces hallucinogenic effects poses a risk to public health. The available and additional evidence, however, is to the contrary: the harm potential of most hallucinogenic compounds like psilocybin and LSD is less than other Schedule I and II compounds and many Schedule III and IV compounds.

3. The Proposed Rule Provides No Substantial Evidence of Actual or Relative Potential For Abuse.

Neither the proposed rule nor the supporting materials present *substantial* evidence of actual or potential for abuse to warrant control. Actual or potential abuse requires more than isolated or occasional non-therapeutic purposes. To show actual or relative potential abuse, there must exist a *substantial* potential for the occurrence of significant diversion from legitimate channels, *significant use* by individual's contrary to professional advice, or *substantial capability* of creating hazards to the health of the user or the safety of the community. *See Grinspoon v. DEA*, 828 F.2d 881, 893 (1st Cir. 1987); House Report at 35. The House Report further explains:

> In speaking of "substantial" potential the term "substantial" means *more than a scintilla* of *isolated abuse*, but less than a preponderance. Therefore, documentation that, say, several hundred thousand dosage units of a drug have been diverted would be "substantial" evidence of abuse despite the fact that tens of millions of dosage units of that drug are legitimately used in the same time period. The normal way in which such diversion is shown is by accountability audits of the legitimate sources of distribution, such as manufacturers, wholesalers, pharmacies, and doctors

For at least some of the Five Tryptamines, DEA has concluded a potential for abuse based on a scintilla of isolated abuse. Therefore, based on the evidence described above, DEA's conclusion runs "counter to the evidence before the agency." *State Farm*, 463 U.S. at 43. And to the extent DEA relies on "potential for abuse" as a basis to schedule the Five Tryptamines, DEA fails to analyze *relative* potential for abuse as the statute requires. *See, e.g.*, 21 U.S.C. § 812(b)(1)(A) (high potential for abuse); *id.* § 812(b)(3)(A) (has a potential for abuse less than the

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[10] Schedules of Controlled Substances: Maintaining Marijuana in Schedule I of the Controlled Substances Act, Background, Data, and Analysis: Eight Factors Determinative of Control and Findings Pursuant to 21 U.S.C. 812(b) at 36 (DEA July 2016)

drugs or other substances in Schedules I or II); *id.* § 812(b)(4)(A) (has a potential for abuse less than the drugs or other substances in Schedule III).[11]

4. Whether Lack of Medical Use is Dispositive of a Classification.

Currently, DEA treats medical usefulness as the controlling factor in classification decisions. Any drug with a potential for abuse with "no currently accepted medical use" is placed in Schedule I. *See, e.g.*, 86 Fed. Reg. 44271 (Aug. 12, 2021). This approach, however, is contrary to the text and the decision by the D.C. Circuit Court of Appeals in *NORML*. *See Nat'l Org. for Reform of Marijuana L. (NORML) v. DEA*, 559 F.2d 735, 748 (D.C. Cir. 1977) ("placement in Schedule I does not appear to flow inevitably from lack of a currently accepted medical use").

As the *NORML* court explained, DEA has more flexibility and discretion in scheduling substances, and it can place the Five Tryptamines (or any drug lacking a currently accepted medical use) in a schedule other than Schedule I. The CSA "contemplates balancing of medical usefulness along with several other considerations, including potential for abuse and danger of dependence." *Id.* "To treat medical use as the controlling factor in classification decisions is to render irrelevant the other 'findings' required by Section 202(b)." *Id.*

Here, even if the Five Tryptamines lack a currently accepted medical use, one or more of them may be appropriately and reasonably placed in a lower schedule. DEA may conclude, in its reasoned judgment, that (a) the Five Tryptamines do not have the same potential for abuse or harm as drugs currently listed in Schedule II such as cocaine, methamphetamine, fentanyl, and PCP; and (b) abuse of the Five Tryptamines would not lead to "severe psychological or physical dependence" but "may lead to moderate or low physical dependence or high psychological dependence," such that Schedule II or III is a more appropriate placement under the circumstances.

5. Non-compliance with § 603 and 604 of the Regulatory Flexibility Act.

The Administrator's § 605 certification is deficient. Although the certification speculates about the effect the proposed rule may have on 31 *suppliers* of the Five Tryptamines, it makes no attempt to analyze the economic impact on other entities, including small entities that use these drugs in scientific and medical research. Because the Administrator "entirely failed to consider an important aspect of the problem," *State Farm*, 463 U.S. at 43, the certification is invalid.

Petitioners request initial and final regulatory flexibility analyses under § 603 and § 604. Such analyses would include a description of the reasons why action by the agency is being considered and alternatives to the proposed rule which accomplish the stated objectives of applicable statute and which minimize any significant economic impact of the proposed rule on small entities. Petitioners specifically request the agency consider two alternatives aligned with the objectives of the CSA that would permit DEA to control abuse and diversion while minimizing

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[11] *See, e.g.*, Basis for the Recommendation to Schedule Tramadol In Schedule IV of the Controlled Substances Act at 12-13 (HHS Sept. 16, 2010) (performing a *relative* abuse potential analysis and concluding that tramadol produces limited reinforcing effects, consistent with a lower schedule) *available at* https://www.regulations.gov/document/DEA-2013-0010-0005.

the economic impact the proposed rule would have on small entities conducting legitimate research, such as Petitioners:

a. Whether DEA could regulate the Five Tryptamines as analogues under the Federal Analogue Act. *See* 21 U.S.C. § 813 ("A controlled substance analogue shall, to the extent intended for human consumption, be treated, for the purposes of any Federal law as a controlled substance in Schedule I."). According to the HHS evaluations, all Five Tryptamines are analogues of other Schedule I substances and produce substantially similar pharmacological effects to those scheduled substance. It is unclear why continued regulation under the Federal Analogue Act could not obtain the objectives of the CSA.[12]

b. Whether DEA could effectively curb abuse and diversion by placing the Five Tryptamines in a lower schedule, either by recognizing that the Five Tryptamines have a "currently accepted medical use with severe restrictions" in medical and scientific research, or by not treating the lack of a currently accepted medical use as dispositive. Notably, placement of these substances in Schedule II would align with recent public statements from DEA and other agencies in the Biden-Harris Administration made in December 2021 regarding relieving research restrictions into controlled substances.

Conclusion

For the reasons stated herein, Petitioners request DEA withdraw or delay the proposed rule.

Alternatively, Petitioners request that DEA (1) update the 2012 HHS evaluation, (2) conduct a Regulatory Flexibility Analysis, and (3) hold a formal rulemaking hearing. In the event DEA ultimately concludes that the Five Tryptamines should be controlled, Petitioners request DEA place the Five Tryptamines in Schedule II or below.

All notices to be sent pursuant to the proceeding should be addressed to Petitioners:

Matt Baggott Tactogen Inc 3790 El Camino Real Unit #510 Palo Alto, CA 94306 matt@tactogen.com	Dillan DiNardo Kykeon Biotechnologies Inc. 1900 Main Street Suite 241 Canonsburg, PA 15317 dillan@mindstate.design

[12] *See, e.g.*, 52 Fed. Reg. 2221 (Jan. 21, 1987) (noting that finalization of rules placing tiletamine into schedule I was not warranted at the time because "persons engaged in activities prohibited by the CSA [could] be prosecuted if those activities involve tiletamine, pursuant to [the Federal Analogue Act]" and delaying scheduling could "accommodate legitimate industry in the production and marketing of a Food and Drug Administration approved drug product").

With copies to:

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Respectfully yours,

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