IN THE UNITED STATES DEPARTMENT OF JUSTICE

DRUG ENFORCEMENT ADMINISTRATION

IN THE MATTER OF	§	
	§	
	§	Docket No. 22-15
Scheduling 4-OH-DiPT, 5-MeO-AMT,	§	
5-MeO-MiPT, 5-MeO-DET, and DiPT	§	
	§	

MINDSTATE DESIGN LABS AND TACTOGEN'S PREHEARING STATEMENT[1]

I. ISSUES[2]

A. Issues of Law

- Whether a finding that a substance lacks accepted medical use is dispositive of a classification, or phrased differently, whether a substance having a potential for abuse less than "a high potential" and has no currently accepted medical use in treatment in the United States can be lawfully placed in any schedule or in any schedule other than Schedule I?

- What does "actual" or "potential for abuse" mean?

- Whether DEA can gather and opine on additional medical and scientific evidence not presented to it in the HHS evaluation.

- Whether the medical and scientific findings in the HHS evaluation bind DEA's position in these proceedings.

- Whether DEA has complied and must comply with the Regulatory Flexibility Act and consider alternatives before moving forward with a final rule.

- Whether DEA complied with the CSA in initiating and maintaining this rulemaking, for at least the reasons previously discussed in the Motion for Summary Disposition papers.

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[1] This filing uses the "Research Companies" to refer to Mindstate Design Labs and Tactogen, Inc

[2] Only factual evidence and expert opinion should be presented at the evidentiary hearing. *See* 21 C.F.R. § 1308.42.

- Whether the agency proceedings in this case violates the Fifth Amendment (i.e., as-applied).

- Whether § 811(b) violates the non-delegation principle because the statute provides no guiding intelligible principle on whether and how long DEA must act on an HHS recommendation when received. *See* Order Denying Mot. for Summary Disposition at 10-18 (no guiding intelligible principle in statute on when agency should institute rulemaking); *Jarkesy v. SEC*, No. 20-61007 (5th Cir. May 18, 2022) (no guiding intelligible principle in statute on how agency should exercise enforcement discretion).

B. Issues of Fact or Fact/Law

- Whether and to what extent a drug that is not a new drug in relation in action to a drug or other substance already listed as having a potential for abuse shows actual or relative potential for abuse.

- Whether substantial evidence shows any of the Five Tryptamines[3] have actual or relative potential for abuse, or a substantial capability to cause a hazard to public health.

- Whether any of the Five Tryptamines have less than a "high potential for abuse."

- Whether any of the Five Tryptamines are "*new* drugs so related in [their] action to a drug or other substance already listed as having a potential for abuse."

- In what schedule, if any, should each of the Five Tryptamines be placed.

II. REQUESTED RELIEF

- For each of the Five Tryptamines, a finding that DEA has not met its burden of showing a "high potential for abuse."

- For each of the Five Tryptamines, a recommendation and finding that DEA has not met its burden of showing that each of the Five Tryptamines should be placed into Schedule I.

- Alternatively, for each of the Five Tryptamines, a recommendation and finding that DEA has not met its burden of showing a Schedule I classification but may meet the criteria for a lower schedule.

[3] 4-OH-DiPT, 5-MeO-AMT, 5-MeO-MiPT, 5-MeO-DET, and DiPT.

III. PROPOSED STIPULATIONS OF FACT

- None of the Five Tryptamines is a product currently approved by FDA or is an ingredient in a product currently approved by FDA.

- Psilocybin, N,N-diethyltryptamine (DET), 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), Methoxy-N,N-diisopropyltryptamine (5-MeO-DiPT), Alpha-methyltryptamine (AMT), N,N-dimethyltryptamine (DMT), 4-methyl-2,5-dimethoxy-amphetamine (DOM), and Lysergic acid diethylamide (LSD), are Schedule I controlled substances.

- For each of the Five Tryptamines, there is no evidence of diversion from legitimate drug channels.

- For each of the Five Tryptamines, there is no evidence the drug produces physiological dependence following acute or chronic administration.

IV. WITNESSES AND SUMMARY OF TESTIMONY

The Research Companies proposed witness list and summary of testimony is listed in **Appendix A.**

V. DOCUMENTS

The Research Companies proposed documents is listed in **Appendix B.**

The Research Companies note that DEA is improperly withholding records duly requested under the Freedom of Information Act. The Research Companies reserve the right to supplement the record with documents if and when they are produced by the agency.

VI. POSITION REGARDING SITUS

The most appropriate venue for the hearing is in the Arlington, VA hearing facility. The Research Companies request permission to present all non-party witnesses outside a 100-mile radius remotely for convenience and/or necessity.

In particular, Dr. Nutt lives in England and is over the age of 70 and therefore may not be able to travel and therefore, may only be able to testify remotely. Dr. Averill is expecting and may not be able to travel and therefore, may only be able to testify remotely.

VII. OTHER MATTERS

A. Subpoena

The Research Companies request a subpoena to at least one witness or representative in FDA's Center for Drug Evaluation and Research to testify at the hearing. Much of the dispute has surrounded whether and to what extent the HHS evaluation and recommendation might be different if DEA sought and obtained an updated evaluation considering the updated science surrounding psychedelics. For example, the Tribunal noted that whether "the HHS information is substantively outdated and whether its recommendation constitutes substantial evidence in favor of scheduling the five tryptamines" is an issue "properly explored at a merits hearing." Order Denying Mot. for Summary Disp. at 15.

The Interested Parties should therefore be able to examine at least one witness from FDA at the evidentiary hearing. This is especially true considering that Congress made the "expert as to the scientific and medical matters at issue in [a] scheduling decision." 76 Fed. Reg. at 77,335. Precedent indicates that the Research Companies should be able to subpoena at least one witness from FDA. *See also* 76 Fed. Reg. at 77,336 at n.8 (Administrator rejecting Meda's argument that FDA review is "entitled to very little weight" in part because Meda did not seek "to subpoena any of the FDA officials who were involved in the review.")

B. Additional Disclosure

The Research Companies request the Tribunal compel targeted disclosure of e-mails and documents reflecting DEA's process in this case. The Tribunal's Order denying summary disposition concludes that "there are any number of reasons why DEA may not have acted during that time frame." It also recognizes that there could have been "an internal, unpublished decision not to schedule a substance." The Research Companies seek limited disclosure on why there was

a ten-year delay in DEA's deliberative process, and if prior to 2021, there was an internal, unpublished decision not to schedule the Five Tryptamines.[4]

The Research Companies have requested adjudicatory records (i.e., authorities) that relate to prior scheduling proceedings that have not been produced by DEA under the FOIA because they allegedly raise "unusual circumstances." The delayed production of these judicial records causes the Research Companies prejudice. The Tribunal should order DEA to produce them.

C. Admissibility of Components of DEA 2021 Eight Factor Analysis

DEA's Eight Factor Analysis, to the extent it contains medical and scientific recommendations that was not evaluated by HHS, should be excluded for the reasons stated in the Motion for Summary Disposition briefing. Section 811(b) makes HHS recommendations and findings on DEA on scientific and medical matters binding within these proceedings. "All *other* relevant data" neither permit DEA to supplement the HHS evaluation with its own medical and scientific findings, nor does it allow DEA to supplement its determination (before or during the proceedings) with medical and scientific evidence not evaluated by HHS. According to the text, structure, and legislative history, "all other relevant data" is a phrase Congress included so that in exercising discretion under the CSA, the Attorney General could consider data that relevant to law enforcement or policy considerations different than the factors listed in Section 811(c), such as the practicalities of enforcement.[5]

The Research Companies propose excluding the highlighted portions of the 2021 DEA Eight Factor Analysis attached as **Exhibit A** to their Motion to Supplement filed on May 9, 2022.

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[4] The Research Companies, through counsel, submitted FOIA requests to DEA.

[5] The Research Companies previously raised this issue. *See* Order Denying Mot. for Summary Disp. at 15 n.16.

D. Order of Proceedings

The Government should present first, followed by the Interested Parties, and the Government's rebuttal.

It would be proper and efficient to submit direct testimony or witness statements through written submissions in advance of the hearing. Doing so can shorten the time needed for the evidentiary hearing. Before cross-examination begins, the presenting party should be able to conduct short direct examination (less than 5 minutes) to introduce the witness and a summary of their written testimony.

Cross-examination should be live but third-party witnesses living more than 100 miles away from the site of the hearing should be able to appear remotely. Several witnesses appearing for the Research Companies may not be able to travel to attend the hearing live. For example, Dr. Nutt lives in England and is over age 70. Dr. Averill is expecting.

The Research Companies would like to discuss allotting time to discuss specific items of evidence on the record and how to handle opening/closing statements, if any.

VIII. TIME ESTIMATE

With written statements, the Research Companies estimate that their case will take no longer than one full day. With live direct testimony, the Research Companies estimate that their case will may take up to four days, exclusive of cross examination.

The Research Companies estimate that their cross-examination of Dr. Carbonaro will take a full day.

Date: June 1, 2022

Respectfully submitted,

/s/ Matthew C. Zorn

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CERTIFICATE OF SERVICE

On June 1, 2022, I served a copy of this document via email to the DEA Judicial Mailbox (ECF-DEA@dea.gov) and the Government Mailbox at (dea.registration.litigation@dea.gov) and: (1) John E. Beerbower, Esq., Counsel for the Government, via email at John.E.Beerbower@dea.gov and to the DEA Government Mailbox at dea.registration.litigation@dea.gov; (2) David Heldreth, CEO of Panacea Plant Sciences, via email at davidh@panaceaplantsciences.net; (3) John T. Hunter, Esq., Counsel for Jason Wallach and Hamilton Morris, via email at john@hljdefense.com; (4) Matt Baggott, Tactogen Inc., via email at matt@tactogen.com; (5) Dillian DiNardo, Kykeon Biotechnologies Inc., via email at dillan@mindstate.design; (6) Graham Pechenik, Esq., Counsel for Tactogen Inc. and Kykeon Biotechnologies Inc., via email at graham@calyxlaw.com.).

/s/ Matthew C. Zorn

Appendix A

Lynnette Averill, PhD

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Dr. Averill is a clinical neuroscientist & psychologist studying neurobiological signatures of suicidality and trauma. She is an Associate Professor of Psychiatry and Behavioral Sciences and Clinical Research Psychologist at Baylor College of Medicine and the Michael E. DeBakey VA Medical Center and an adjunct Assistant Professor at Yale School of Medicine and the Clinical Neuroscience Division of the VA National Center for PTSD. Dr. Averill qualifies as an expert in clinical neuroscience and psychology.

Dr. Averill will explain how there is a mental health crisis in this country and that limited effective pharmacologic treatments exist for stress and trauma-related concerns such as PTSD, depression, and suicidality. She will explain that there are only two FDA-approved medications indicated for PTSD, both selective serotonin reuptake inhibitors (SSRIs) and the landscape of effective treatment is even bleaker for suicidal thoughts and behaviors. She will explain that fewer than half of the patients achieve full remission on SSRIs and that the rates of non-response or partial response to these medications among combat-exposed individuals, particularly those with chronic PTSD, are comparable or worse to those of civilian patient populations. She will testify that these approved therapies, even when effective, are slow-acting, requiring weeks to months before patients experience clinical benefit and also have a significant side effect profile.

Dr. Averill will testify to the urgent need to investigate novel therapeutics with potential to offer relief and healing to individuals who do not respond to current treatments or require rapid relief. She will explain how psychedelic medicines are promising drugs that work significantly

more rapidly than traditionally available pharmacological interventions, such as SSRIs. In particular, she will explain how two Schedule I drugs, MDMA and psilocybin, are fast-acting therapeutics that rapidly improve functioning and produce robust improvements. She will testify that while there are concerns about abuse potential of these substances, neither empirical research nor clinical anecdotes support this as a major concern, especially considering the cost benefit analysis comparing the low potential for abuse relative to the risk for continuing with ineffective treatments. She will explain the mounting body of literature that psychedelic therapies are safe, effective, and rapid acting.

Dr. Averill may testify about the quality of the psychedelic experience and how that contributes to clinical benefit, specifically, how agonism at serotonin receptors that contribute to psychedelic or hallucinogenic effect – the disconnect from reality, the dissociation, hallucination, and/or significant mystical or spiritual experience – may contribute to positive or transformative outcomes and permit changes in the brain. Dr. Averill will testify that it is unlikely that rodents would have experiences similar to those to which humans attribute deep personal meaning and positive, therapeutically relevant mood and behavioral change after taking a psychedelic.

Dr. Averill will testify on the first generation of psychedelic therapies and explain their disadvantages, such as multi-hour dosing sessions and side-effects. For example, she will explain that the current psychedelic therapies that have attained breakthrough status are intensive interventional treatments, have 6 to 8 hours of duration, and require medical monitoring during that period. Dr. Averill will testify that second generation psychedelic therapies are needed to improve upon first generation therapies and add to the toolbox of available interventions, and critical to that is research. Dr. Averill will also testify about development of psychedelic therapies to address other conditions traumatic brain injury, stroke, and even Alzheimer's disease. She will

also explain how psychedelic medicines and assisted therapies are not a “one size fits all.” She may also testify about future research needs with psychedelics, including how to these interventions in concert with the other tools and established therapies.

Andrew Chadeayne, PhD.

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  Issaquah, Washington, 98027

Andrew Chadeayne is the founder and CEO of CaaMTech, Inc., a drug discovery and development company focused on engineering psychedelic drugs that meet the standards of modern medicine. Dr. Chadeayne published work in the neuroscience of addiction and reward at Princeton University, has a Ph.D. in chemistry from Cornell University (2006), and graduated cum laude J.D. from George Washington University Law School, where he won the American Bar Association's Award for Excellence in Intellectual Property.

Dr. Chadeayne and his research teams have authored dozens of papers on the structure and pharmacology of tryptamine compounds and synthesized and characterized hundreds of analogues of controlled substances. Dr. Chadeayne will testify about his company's partnership with NIDA's Designer Drug Research Unit (DDRU), which aims to thoroughly investigate the pharmacology of new psychoactive substances, including researching tryptamine-based substances and their pharmacological effects. Dr. Chadeayne qualifies as an expert.

Dr. Chadeayne also will testify that structural similarity between two compounds, including two tryptamine compounds, is not a reliable indicator of similarity in pharmacological effects. Dr. Chadeayne will testify that two tryptamines can have close structural relationships without exhibiting the same in vitro or in vivo pharmacology. Dr. Chadeayne will also testify that recent scientific and medical research since 2012 has clarified our understanding that stimulation of 5-HT2A receptors alone, without assessment of other aspects (such as stimulation of other receptors, pharmacokinetics, and animal models like the Head Twitch Response), cannot accurately predict a drug's pharmacological effects or similarity to other hallucinogenic drugs.

David Nutt, DM, FRCP, FRCPsych, FSB, FMedSci

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Dr. Nutt is the Professor of Neuropsychopharmacology and director of the Neuropsychopharmacology Unit in the Division of Brain Sciences at Imperial College. Dr. Nutt studied medicine at Downing College, Cambridge, graduating in 1972. Dr. Nutt spent two years as Chief of the Section of Clinical Science in the National Institute of Alcohol Abuse and Alcoholism in NIH, Bethesda, USA. On returning to England in 1988 he set up the Psychopharmacology Unit in Bristol University before moving to Imperial College London in December 2008 where he leads a similar group with a particular focus on brain imaging especially PET. Dr. Nutt has edited the Journal of Psychopharmacology for over two decades and acts as the psychiatry drugs advisor to the British National Formulary. He has published over 400 original research papers as an author or co-author, a similar number of book reviews and chapters, eight government reports on drugs and 27 books.

Dr. Nutt is currently Chair of DrugScience, the British Neuroscience Association (BNA) and the British Association of Psychopharmacology (BAP). In addition, he is a Fellow of the Royal Colleges of Physicians and of Psychiatrists and a Fellow of the Academy of Medical Sciences. He is also the UK Director of the European Certificate and Masters in Affective Disorders Courses and a member of the International Centre for Science in Drug Policy. Dr. Nutt qualifies as an expert in pharmacology and drug abuse.

Dr. Nutt will testify that psychedelic drugs remain a controversial issue among the public and politicians, tainted by previous stigmatization and perceptions of risk and danger. Dr. Nutt

may testify about his work history for the UK government on the Advisory Council on the Misuse of Drugs and the circumstances surrounding his release.

He will testify that large body of research from the 1950s and 1960s reported largely positive effects and a lack of adverse clinical effects with psychedelics. Dr. Nutt will testify that psychedelics have come a long way since the first wave of experimentation and research and that while their potential range of psychological and psychiatric, as well as physiological risks remains to be fully understood, the physiological safety of psychedelics is by now relatively well established, and they have been described as one of the safest known classes of Central Nervous System drugs.

For example, he will testify about his recent paper "Adverse effects of psychedelics: From anecdotes to misinformation of systemic science" published in the Journal of Psychopharmacology. Among other things, citing significant research since the 1970s, the paper concludes that hallucinogens have low potential for abuse compared to other controlled substances, that the characterization of psychedelics as addictive is based on misinformation and misunderstanding, and that today, these compounds are more often discussed in terms of their anti-addictive properties.

Dr. Nutt may testify that the fact that any tryptamine is a synthetic analogue of other tryptamines alone says little about its pharmacological action. Dr. Nutt will testify about research showing that with psychedelics consistently shows positive personality changes or increases in well-being. Dr. Nutt will testify that adverse events reported from use of multiple drugs is not a reliable indicator of the danger that might be posed by a particular drug. He may also testify that responses to psychedelics are difficult to predict.

Dr. Nutt will note the major difference in the abuse potential associated with psychedelics, as compared with other substances that carry a high risk of compulsive pattern of repetitive use and abuse. Many psychedelics are associated with a lower propensity to frequently and repeatedly self-administer, and that drugs commonly accepted as having hallucinogenic properties are not self-administered by laboratory animals. He will also testify research with psychedelics typically produces a low incidence of adverse events. Dr. Nutt will also testify that serotonergic psychedelics have been shown to be safe under medical supervision.

Dr. Nutt will testify that in comparison with other psychoactive drugs, psychedelics score consistently low in their abuse potential. For example, he will testify that psilocybin carries a lower dependence risk than caffeine and being among the lowest risks of death of all major substance abuse categories. Psychedelics or serotonin agonists generally carry a lower dependence and abuse risk when compared to other drug classes such as amphetamines, benzodiazepines, opiates, and other dopaminergic drugs. Dr. Nutt will also testify that psychedelic or hallucinogenic drugs do not rank as drugs that are harmful to others. Dr. Nutt will testify about his analysis that measures the risk to an individual, and the damage to society as a whole and explain that psychedelics rank relatively low.

Dr. Nutt may also testify about the history of psychedelic and psychedelic-assisted therapy research. He will testify about early research that showed the usefulness of psychedelics with those having anxious, obsessive and depressive states. He will also testify that such research produced a low incidence of adverse events.

Shane Pennington, J.D.

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Mr. Shane Pennington is counsel for Vicente Sederberg LLP. Mr. Pennington has a J.D. from the University of Texas School of Law. Before entering practice, Mr. Pennington clerked for Judges David Sentelle (D.C. Cir.), Jennifer Elrod (5th Cir.), and Royce Lamberth (D.D.C.). Mr. Pennington has an active law practice advising clients on federal psychedelics law, including DEA regulations governing registration to handle schedule I psychedelic substances under the Controlled Substances Act. Mr. Pennington regularly litigates issues with important implications for the federal regulation of psychedelics before federal appellate courts across the country and both speaks and publishes on issues related to administrative law, and specifically, the Controlled Substances Act. Mr. Pennington will testify as an expert in federal controlled substances regulation and history.

Mr. Pennington will testify on regulatory obstacles to researching and administering psychedelic medicines, particularly Schedule I substances. He will explain that the schedule I status of psychedelics is a significant legal barrier to research, development, and understanding psychedelic compounds. He will testify how in 1950s and 60s, scientific research on psychedelics was permitted; he may also explain how that changed with the CSA and war on drugs in the 1970s.

Mr. Pennington will testify that how Schedule I status has impeded and impedes development of clinical psychedelics. Mr. Pennington will explain that Schedule I status drives up the cost of manufacture, storage, and administration of a drug or substance and can make researching Schedule I substances (or using Schedule I substances in research) prohibitively expensive for smaller entities. He may explain that the current paradigm sets up a catch-22 for research with Schedule I substances where DEA requires scientific evidence of efficacy obtained

from large, well-controlled clinical trials; but Schedule I classification impedes completion of such trials. Mr. Pennington may testify that, although Congress did not intend to not to unduly hamper research with the CSA, that has happened in practice.

Mr. Pennington will testify how Schedule I regulation stifles innovation, makes it so that well-capitalized private companies fund most research on psychedelics, and the Schedule I status and the cost of overregulation contributes to anti-competitive practices. Mr. Pennington will testify that the public health problems that psychedelics may address, such as the opioid epidemic, such that it is preferable to have a diverse array of scientists and other stakeholders shaping the narrative and steering public policy.

Mr. Pennington will testify that when Congress enacted the CSA, it gave primary responsibility for research into the medical, pharmacological, and social aspects of drug use and abuse with the Department of Health, Education, and Welfare. He will explain that there was considerable concern in 1970 over whether HEW or DOJ should have control over research. He will testify that the Senate and House Bills differed in that the Senate Bill only required BNDD to solicit advice from HEW, while the House Bill made HEW's advice on scientific and medical matters binding. He will testify that the statute and legislative history reflects a division of labor between HEW and DOJ with HEW having primacy on medical and scientific decisions. Mr. Pennington will testify that enforcement or danger to public health is one of the most critical factors in arriving at a determination of whether a drug should be controlled. He will testify that potential for abuse encompasses legal and medical/scientific considerations.

Mr. Pennington will testify that the intent of the Controlled Substances Act schedules was to be flexible and allow for swift administrative action and decisions based on current knowledge to meet a national problem. He will further testify that if new information provided to research and

law enforcement agencies (such as an abatement in abuse) regarding a drug was provided, the intent of the law would be to down schedule such drug.

Mr. Pennington will discuss that drugs without currently accepted medical uses are in other schedules. For example, Mr. Pennington will explain that Congress was aware of morning glory seeds and in 1970 but placed their active hallucinogenic constituent (and LSD analogue) in Schedule III. Mr. Pennington may also testify about hallucinogenic compounds that are not scheduled (e.g., nutmeg). Mr. Pennington will also testify that Congress has put drugs lacking currently accepted medical uses in other schedules. Mr. Pennington may further discuss the 2017 HHS decision to recommend scheduling Kratom and it rescinding that recommendation due to a need to further evaluate the scientific evidence. Mr. Pennington will testify that historically, DEA and HHS has looked to current evidence of actual abuse and has looked at factors such as ease of acquisition and routes of administration in determining whether a drug or substance has a "high potential for abuse."

Mr. Pennington will testify about the Federal Analogue Act. Mr. Pennington will testify that the Federal Analog Act automatically prohibits a chemical if it is "substantially similar in structure" to an already-prohibited drug, and has a "substantially similar chemical effect" or is "represented to have such an effect." Mr. Pennington will explain that the purpose of the "Federal Analogue Act" was to control "designer drugs," or pharmaceutical products that slightly differ from scheduled substances that for one reason or another, made their way onto the black market. Mr. Pennington will explain how the Analogue Act works as-applied to the Five Tryptamines and how the Analogue Act operates to reduce or lowers their potential for abuse.

Matthew Baggott, PhD

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Dr. Baggott is the CEO and co-founder of Tactogen Inc, a public benefit corporation developing novel medicines for treating mental health problems. Matthew is a neuroscientist, data scientist, and psychedelic researcher, with over 30 years' experience studying how psychedelics can be made safer and more therapeutic. Before founding Tactogen, Dr. Baggott worked at Genentech running a team of data scientists and engineers.

Dr. Baggott will testify about his experience and his qualifications as an expert. He has published dozens of papers going back to the early 1990s relating to the study of psychoactive substances. He has published extensively on MDMA, MDA, and other drugs such as alcohol, cocaine, and ketamine. He has also worked in labs that have conducted studies using methamphetamine and LSD.

Dr. Baggott will testify about his background working with psychedelics, including his undergraduate studies and work afterward at the University of Chicago working with rat psychopharmacology and his postgraduate work at the University of California, San Francisco and California Pacific Medical Center conducting human psychopharmacology studies.

Dr. Baggott will explain that 5-HT (serotonin) acts as a neuromodulator signal throughout much of the brain, adjusting the stability of ongoing brain processes in response to changing environmental influences, and affects sensory and other neurons. He will explain that the 5-HT2A receptor is thought to be responsible for hallucinogenic effects, that recent research has identified limitations in using binding at 5-HT2A to predict and understand such hallucinogenic effects, and that the ability to bind doesn't always mean the ability to stimulate or produce specific effects of interest. In addition, effects at other receptors can significantly modify effects of a 5-HT2A

agonist. He may describe drug administration studies that show how the effects of 5-HT2A agonists are modified by stimulation or blockade of other receptors. He will therefore testify that the effects of hallucinogens cannot be reliably determined by looking at 5-HT2A alone, but require looking at effects on other receptor sites, such as 5-HT1A and 5-HT1B that can contribute to sensory and other neural processing. He may testify that features can get lost in translation when applying conventional frameworks.

He will testify that hallucinogens and drugs that act on that 5-HT2A vary. While many produce profound dramatic visual alterations, others do not. He may testify that whether a hallucinogenic effect contributes to the benefit of the drug is up for debate, and his opinion that it is one of several factors and that studies show relationships between therapeutic benefit and nature of the experience. In addition, he may explain that even challenging experiences can result in improved well-being in the end, and seemingly adverse effects can contribute to positive lasting effects. Dr. Baggott will testify that in his opinion, psychedelic science has developed considerably in the past decade, and properly accounting for the factors enumerated in 21 U.S.C. § 811(c) would require accounting for these modern medical and scientific frameworks and newer medical and scientific evidence.

Dr. Baggott will testify about the state of science with psychedelics and how it has evolved since the 1970s and since 2012. He will testify that the science on psychedelics from the 1970s is now outdated as it was based on a small number of compounds and limited methods of making scientific measurements. He will explain that psychedelic science indicates 5-HT2A agonists do not neatly fit the abuse liability assessment frameworks used to evaluate other classes of drugs. Those in the art sometimes use different metrics to measure experience and neural effects.

Dr. Baggott will testify about Tactogen and why he started the company. He will explain that more than half of all people experience mental illness in their lifetime and that most do not receive adequate treatment for their conditions. He will testify about the value of psychedelics in psychotherapy, not just for traumatic conditions.

Dr. Baggott will explain how he worked on MDMA decades ago—including the first federally funded study administering MDMA to healthy volunteers—and how the science on MDMA was misunderstood when MDMA was placed in Schedule I. Dr. Baggott will explain how he helped do a comprehensive literature review of MDMA for submission to FDA by the nonprofit organization MAPS. He will explain how research with MDMA has progressed, despite regulatory difficulties, and has been named a breakthrough therapy by FDA for treating PTSD. Dr. Baggott will testify about certain shortcomings with MDMA, including short term hypertension and long-term tolerance. Dr. Baggott will thus explain that one of the reasons he started Tactogen is to develop alternative treatments with fewer side effects that can be used in people and contexts where the MDMA therapy is not ideal, for example, in situations where a less powerful experience or a take home therapy is beneficial. For this reason, Tactogen is working to develop synthetic molecules that may complement MDMA and classical psychedelics that are currently in development.

Dr. Baggott will testify about how Tactogen, and those with whom Tactogen works, go about discovering, inventing, or researching new therapies. Specifically, he will explain how Tactogen uses existing knowledge and new data to build statistical models to predict the biological effects of molecules, conducts in vitro assays ,uses animal models, and evaluates compounds at approximately 50 different binding sites instead of just looking at 5-HT2A activity. Dr. Baggott may testify that this analysis is not difficult to do with budget and time.

Dr. Baggott may testify how his company's methods are standard in the 2022 art and surpasses the evaluations conducted by HHS and DEA. He may also testify that a credible analysis in the art today would look at pharmacological effects at several binding sites to understand psychoactivity.

Dr. Baggott may testify that the Eight Factor analysis does not achieve the level of scientific rigor that he would expect from scientists in this field in 2022. For example, he will explain that agonism should be measured at more than a single receptor and that additional receptors and signaling pathways are important. As an example, Dr. Baggott may discuss lorcaserin, a 5-HT2A agonist, which HHS and DEA concluded should be placed in Schedule IV. As another example, Dr. Baggott may discuss quipazine, a 5-HT2A agonist that is identified as hallucinogenic using in vitro and animal assays but which is not used as a hallucinogen by humans.

Dr. Baggott will testify that drug resemblance does not reliably translate to similar pharmacological effect. He will explain that receptors in the brain are tuned to detect small differences in molecules and that molecules we perceive to be structurally similar are not necessarily considered by the brain to be similar. Dr. Baggott may specifically apply this testimony to the specific tryptamines at issue. For example, in terms of effects in humans, he may say that 4-HO-DiPT and DiPT are structurally similar but are not alike in pharmacological effect.

Dr. Baggott will testify that Tactogen works with a number of collaborators, both formal and informal, to assist in research and development. He will explain that most collaborators don't have Schedule I licenses. He will explain that most assays aren't run within the company but are run by commercial partners, which is typical of most small pharma companies. Dr. Baggott may opine that DEA placing tryptamine analogues in Schedule I makes the US less competitive without adequate justification in that the resulting regulations create substantial overhead on startups and

other US companies. These overheads include both additional time needed to obtain approvals and additional expenses associated with storing even small amounts of Schedule I compounds. As a result, companies in other jurisdictions have competitive advantages.

Dr. Baggott may testify that adverse events from polydrug use are not indicative of effects of single drug use.

Dr. Baggott will testify that the Five Tryptamines have less potential for abuse than benzodiazepines, methamphetamine, cocaine, and other substances that are not Schedule I. He will testify that the Five Tryptamines do not have high potential abuse.

Dr. Baggott will testify on how analogues are used in research beyond pharmaceutical development, specifically, how previously known analogues as comparison points to establish how new chemicals are similar or different to known entities. In addition, Dr. Baggott may discuss how analogues are used as tools for basic research in understanding the brain.

Dr. Baggott will address specific flaws in the Eight Factor analysis relating to drug comparisons. For example, he will testify on the comparison between 5-MeO-MiPT and DOM, the latter of which is highly selective for 5-HT2A receptors. He will testify that such comparison may not add anything to what one could determine from in vitro assays. Dr. Baggott will also offer the opinion that no evidence suggests that 4-OH-DiPT shows sufficiently similar pharmacological responses to DOM and LSD, which are longer acting, to deem the drugs as comparable.

Dr. Baggott will also address the limitations of drug discrimination with psychedelics, particularly how findings in rodents do not always translate to humans. Specifically, he will testify that we do not know the internal cues that animals use to discriminate different drugs and that findings do not always translate and that humans compare across more dimensions. For example, in drug discrimination assays, animals will indicate that fenfluramine feels like MDMA, while

humans do not. Thus, there is a significant risk of false positives. Two molecules in a drug discrimination assay may be similar in humans on some limited dimensions, but not others, and the resulting overall profile in humans may greatly differ.

Dr. Baggott will testify that identifying that a drug may cause euphoria, fatigue, headache, gastrointestinal distress, insomnia, and anxiety is of limited probative value and describes symptoms of many controlled and uncontrolled drugs, not just Schedule I drugs, and many of which are not deemed to have a hazard to the health of the user and to the safety of the community. Dr. Baggott may discuss two such drugs which have 5-HT2A activity: Sustiva, an approved drug that acts on 5-HT2A receptor that is an essential medicine, is not scheduled, but has LSD-like properties; and mefloquine, an antimalarial pill, that shares an in vitro receptor interaction profile with some hallucinogens.

Dillan DiNardo, MBA

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Mr. DiNardo is the CEO and co-founder of Mindstate Design Labs ("Mindstate"), a preclinical stage biotechnology company focused on developing medicines to treat mental health disorders, specifically, 5-HT2a agonists. Mr. DiNardo has a BS and MBA from Robert Morris University.

Mr. DiNardo will discuss how he became interested in founding Mindstate Design Labs. He will testify about Mindstate's mission to investigate the biochemical basis of psychedelic drugs, to examine the diversity of effects among drugs in the class, and to provide more effective therapies for patients with fewer undesirable side effects. He will testify that his company is a top start-up in the space and has secured $11.5 million in seed funding from top-tier investors including Y Combinator, Initialized Capital, and founders of Neuralink, AngelList, Coinbase, Instacart, Rappi, and Twitch to develop its technology.

Mr. DiNardo will explain how Mindstate's research has shown that drug discrimination studies in animals provides little insight into the complexity of the psychedelic experience in humans. He will explain that Mindstate's predictive platform is intended to address this central problem in 5-HT2a agonist development. Mr. DiNardo will testify that its research has shown that not every 5-HT agonist acts similarly. For example, Mr. DiNardo may explain how research shows the drug n,n-DMT causes predictable causes users to go into a non-responsive dreamlike state and produces experiential effects unlike other 5-HT agonists. He may also describe the example of 5-MeO-DMT, which consistently results in oceanic boundlessness. He may explain that n,n-DMT and 5-MeO-DMT are analogues but unlike each other.

Mr. DiNardo will explain that animal models are incapable of showing certain psychological effects in humans, such as oceanic boundlessness. He will explain that Mindstate is developing a predictive platform to draw the links between the chemical data to identify human effects that are therapeutically helpful and unhelpful. As an example, Mr. DiNardo may discuss the auditory effects of DiPT, which tend to be unique but unhelpful in a therapeutic environment. He will testify that Mindstate has catalogued over hundreds of effects from biochemical and human data sets. He will testify that understanding distinctions in this data are important, to prevent abuse, design drugs, formulate policy, and guide capital investment. Mr. DiNardo will testify that he would partner with DEA to help the agency better understand potential adverse effects with psychedelic compounds in order to help inform policy decisions.

Mr. DiNardo will explain Mindstate's research process. He will explain how his company selects candidates by comparing biochemical data to human reports. He will explain how data exists for many analogues already, and that in some cases, the company looks for analogues with a high degree of specificity and combines that drug with a separate drug that does not produce psychedelic effects in order to reproduce a specific experience. Mr. DiNardo will testify that Mindstate, as a start-up business, works with a variety of contract research organizations that have expertise in various areas of drug development.

He will testify that if those CROs are subjected to Schedule I regulatory barrier, it will drastically limit the ability of Mindstate and other small businesses to compete due to the administrative and regulatory burdens. He will further testify about Mindstate seeking to disrupt entrenched pharmaceutical companies that market antidepressants and other drugs for mental and behavioral health treatments by improving the standard of care with safer, more effective, and potentially less frequently administered treatments. He will testify that larger publicly traded

companies may be able to negotiate Schedule I restrictions and be able to scale facilities, which is something smaller businesses like Mindstate cannot as easily do, if at all. He will testify that the company partners with researchers that have specialized and unique skills in areas such as computational neuroscience, neuroimaging, and medicinal chemistry; and that a Schedule I classification would interfere with these relationships.

Mr. DiNardo will testify that the five tryptamine compounds do not show a high potential for abuse, have little to no addiction potential, and are physiologically safe. He will also testify that the science in the drug evaluations is outdated.

Appendix B

Ex.	Description
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4	Averill, Lynnette A, and Chadi G Abdallah. “Investigational drugs for assisting psychotherapy for posttraumatic stress disorder (PTSD): emerging approaches and shifting paradigms in the era of psychedelic medicine.” Expert opinion on investigational drugs vol. 31,2 (2022): 133-137. doi:10.1080/13543784.2022.2035358
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9	Belcher, Sarah. "Here's Why You Shouldn't Do the Nutmeg Challenge on TikTok." Distractify (Apr. 15, 2020)
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16	"FEDERAL DRUG ABUSE AND DRUG DEPENDENCE PREVENTION, TREATMENT, AND REHABILITATION OF 1970," Federal drug abuse and drug dependence prevention, treatment, and

Ex.	Description
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24	Krediet, Erwin et al. "Reviewing the Potential of Psychedelics for the Treatment of PTSD." The international journal of neuropsychopharmacology vol. 23,6 (2020): 385-400. doi:10.1093/ijnp/pyaa018
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