UNITED STATES DISTRICT DEPARTMENT OF JUSTICE

Drug Enforcement Administration

In the Matter of **Scheduling 4-OH-DiPT, 5-MeO-AMT, 5-MeO-MiPT, 5-MeO-DET, and DiPT**	**Docket No. 22-15**

STATEMENT OF DILLAN DINARDO, MBA

My name is Dillan DiNardo. I am the co-founder and CEO of Mindstate Design Labs ("Mindstate"), a preclinical-stage biotechnology company focused on developing small molecule 5HT2a agonists to treat mental and behavioral health disorders. I have a BS and MBA from Robert Morris University. My career began in finance with the large international consulting firms including PricewaterhouseCoopers, Deloitte, and BDO where I primarily worked in mergers and acquisitions. More recently I worked in biotech venture capital, where I invested or took various operational roles in more than 50 biopharma, medical device, and healthtech companies.

I left my role in VC to co-found Mindstate to investigate the biological basis of the enormous diversity of effects among compounds in the class, and to use that knowledge to provide more effective therapies with fewer undesirable side effects for patients. **M&TX 34** is a printout of our website.

The company recently secured an outsized seed funding round of $11.5 million from top-tier investors including the world's top startup accelerator, Y Combinator; the world's top-performing seed-focused VC fund, Initialized Capital; and angel investors including the founders

of some of Silicon Valley's highest-profile companies such as Neuralink, AngelList, Coinbase, Instacart, and Twitch. We are a team of 18 experts in drug development, neuroscience, psychedelic therapy, and computational biology, and our Scientific Advisory Board includes representation from the senior leadership of three of the world's leading academic research centers focused on this therapeutic class. We've been featured by media outlets including The Wall Street Journal, Fortune, Axios, Fast Company, Entrepreneur, Business Insider, Vice, and TechCrunch.

Three years ago, I would never have dreamed that I would leave my VC role and start a company researching psychedelics, but I've now committed all of my effort and my future into Mindstate after seeing the research done over the past few years which has transformed our understanding of this therapeutic class. The effect sizes in late-stage clinical trials are practically unheard of in any disease indication, and this is in the field of psychiatric disorders, the largest unmet need in all of medicine, which hasn't seen a new therapeutic class for over 30 years. Mindstate is my opportunity to help make a dent in the universe – to provide not just symptom management, but actual healing for the life-threatening disorders that every day claim the lives of hundreds of our veterans, police officers, abuse survivors, and victims of the opioid epidemic.

Mindstate's Research and Development

Mindstate's research, as well as the larger body of scientific literature, has shown that drug discrimination studies in animals provide little to no insight into the complexity of the psychedelic experience in humans.

As stated by the Jacob and Shulgin (1984) reference (**GX15** at 74), "With many drug families, the results of animal model studies (steps 2 and 3) can allow prediction of new drug structures (step 1). However, with research in hallucinogenic drugs (where the desired

pharmacological activity can only be demonstrated in humans), the confirmation of activity must occur by necessity in humans."

For example, the research shows that at sufficient doses the 5-HT2a agonist n,n-DMT predictably causes users to go into a non-responsive dreamlike state and produces experiential effects unlike other 5-HT agonists. One of the primary thematic domains in the n,n-DMT literature is the very strange experience of contact with various entities which occurs in approximately half of administrations.[1] In contrast, the 5-HT2a agonist 5-MeO-DMT consistently produces an oceanic boundlessness state. These two substances are analogues of one another and fully substitute in animal drug discrimination studies, but they are completely unlike each other when administered to humans. In human studies, the oceanic boundlessness state is commonly quantified by validated measurement instruments and cited as one of the primary correlates of long-term treatment outcomes.[2] In contrast, as one might expect, it has not yet been established what therapeutic utility the entity contact experiences of n,n-DMT (DMT) might have. These are simply two examples of commonly known serotonergic agonists demonstrating the vast difference in effects and potential therapeutic applications. Hundreds of similar distinctions could be made between various scheduled compounds and the Five Tryptamines.

In short, the literature as well as Mindstate's own research indicates that different serotonergic agonists have very different effects in humans, including different adverse event profiles and therapeutic applications.

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[1] Lawrence, D.W., Carhart-Harris, R., Griffiths, R. et al. Phenomenology and content of the inhaled N, N-dimethyltryptamine (N, N-DMT) experience. Sci Rep 12, 8562 (2022) (available at https://www.nature.com/articles/s41598-022-11999-8).

[2] Roseman L, Nutt DJ, Carhart-Harris RL. Quality of Acute Psychedelic Experience Predicts Therapeutic Efficacy of Psilocybin for Treatment-Resistant Depression. Front Pharmacol. 2018 Jan 17;8:974 (available at https://pubmed.ncbi.nlm.nih.gov/29387009/).

This is a central problem in drug development within this therapeutic class, and a key reason I co-founded Mindstate: animal models are incapable of showing certain psychological effects in humans that occur with use of psychedelics, such as the oceanic boundlessness state I just discussed. Mindstate has catalogued over four hundred distinct effect labels as part of our predictive platform to draw the links between biochemical data and human effects that are therapeutically helpful and unhelpful. For example, one of the Five Tryptamines, DiPT, is a compound that is commonly known to have unique auditory effects, which are remarkable but relatively unhelpful in a therapeutic environment.

I cannot testify specifically about Mindstate's technology without divulging confidential and trade secret information. Generally, Mindstate's method involves collecting data from the human experience and biochemical information from assays, and then applying observed correlations between the two data sets. Data exists for many analogues already. To create a targeted effect profile, the company looks for analogues with a high degree of selectivity for certain receptor targets and combines that compound with another drug that does not produce psychedelic effects.

Understanding the distinctions in this data and among 5-HT2a agonists is important to identify potential for abuse, design drugs, formulate policy, and guide capital investment. To be clear, I'm not testifying at this hearing to be a barrier to the DEA's work to protect public health. Mindstate would be happy to use its predictive models to work with the DEA to help the agency better understand potential adverse effects with psychedelic compounds to help inform policy decisions.

Schedule I Restrictions Limit Research and the Ability of Small Businesses to Compete

Some sources estimate that the total pharmaceutical industry is valued at about 1.27 trillion U.S. dollars. Psychedelic pharmaceutical companies comprise a tiny fraction of this market. The top-5 pharmaceutical companies all have market capitalizations of $250 billion or more. In contrast, the top companies in the psychedelic space have market capitalizations between $400 million and $600 million. The 200th ranked pharmaceutical company is worth more than the most valuable psychedelic pharmaceutical company by market valuation.

For a large pharmaceutical company, these Schedule I regulatory restrictions may be an annoyance. For start-ups and non-profit organizations, however, which is currently most if not all the psychedelic pharmaceutical space, these restrictions can be significant if not crippling.

There are a variety of reasons large pharmaceutical companies do not engage in the research and development of psychedelic therapies. Compared to conventional pharmaceutical products such as antidepressants, psychedelic medicine is a "disruptive" technology. These therapies promise to improve the standard of care with safer, more effective, and potentially less frequently administered treatments. In turn, psychedelic therapies will likely reduce the cost of mental healthcare nationwide and ultimately, taxpayer burdens. Naturally, entrenched pharmaceutical companies probably have little interest in disrupting their own revenue streams.

Because Mindstate is a start-up company, it outsources many of the necessary tasks in pharmaceutical research and development to other service organizations called contract research organizations (CRO). Mindstate currently has relationships with a number of CROs and researchers to further its research and development of unscheduled psychedelic compounds. These organizations have specialized and unique skills in various areas crucial to preclinical development, including in vitro assays, animal testing, and manufacturing. Assuming a drug or substance currently being researched were placed onto Schedule I, it would not be enough for

Mindstate to get a Schedule I license to continue its research. Rather, each CRO or researcher handling a drug or substance would need to get a Schedule I license, which would require each CRO to expend thousands of dollars bringing facilities into compliance, for example, purchasing a Schedule I compliant safe. Even more burdensome than the additional direct cost is the impact on development timelines, which have outsized effects on downstream costs that could be catastrophic for startup businesses including Mindstate. Many CROs are unable or unwilling to undergo the burdensome Schedule I processes, which would result in the need for us to incur substantial cost and delays to find alternative CROs that would likely be less cost-effective and less suited for the particular research purpose.

It is therefore my opinion that placing these compounds on Schedule I not only unnecessarily delays research and development, but would create unnecessary barriers to entry, and discourage potential entrepreneurs from introducing beneficial products and processes. Placing the Five Tryptamines in Schedule I would have a disproportionate impact on small businesses, including Mindstate. Alternative regulatory approaches, such as continuing to regulate the Five Tryptamines as controlled substance analogues, do not conflict with the stated objectives of the CSA and would minimize the negative economic and public health impact. It would be unconscionable to unreasonably delay and possibly doom research on life-saving medicine for life-threatening disorders on account of a negligible number of reported illicit uses of compounds that do not show a high potential for abuse, have little to no addiction potential, and are physiologically safe.

Mindstate's 5-MeO-MiPT Research

Mindstate's research covers dozens of serotonergic agonists, most of which have unique pharmacological profiles and unique phenomenological effects that are suited to particular

therapeutic purposes. Among the compounds proposed for scheduling, our research on 5-MeO-MiPT has progressed the furthest. Mindstate is on the cusp of entering its 5-MeO-MiPT related drug into clinical trials. We have conducted and are currently conducting pre-clinical research with 5-MeO-MiPT, including affinity and functional assays, studies in rats, mice, and dogs, and manufacturing of GMP-compliant material in preparation for human studies. We have chosen to progress 5-MeO-MiPT to human studies specifically because of its uniquely unremarkable effects as compared to other hallucinogens. Informally, 5-MeO-MiPT has been called "psychedelic tofu" in reference to the often comparatively bland nature of its effects at normal doses. This makes the drug uniquely suited to our research and development approach of precision engagement of receptor targets that interact with 5HT2a to maximize therapeutic effects and minimize hallucinogenic and other effects that are therapeutically undesirable.

The DEA Eight-Factor Report notes that 5-MeO-MiPT "elicits pharmacological responses similar to the schedule I substances LSD and DMT." In humans, however, 5-MeO-MiPT is not pharmacologically similar to these substances in a number of ways. 5-MeO-MiPT is orally active; DMT is not.[3] When administered orally, 5-MeO-MiPT has a 3 to 7 hour duration of action. In contrast, LSD administered orally typically lasts 8 to 20 hours. Most importantly, Mindstate's internal wide-scale receptor affinity assays show only a few drugs with a narrow range of receptor interaction. Among those drugs, 5-MeO-MiPT has a uniquely shorter duration of action, which makes the compound suitable for commercially viable therapeutic applications.

The notion that 5-MeO-MiPT has a hallucinogenic effect that is "15-fold more potent than DMT in producing hallucinogenic effects in humans" (page 6 of the DEA Eight-Factor

[3] Jacob and Shulgin (1980) (**GX15** at 281) notes that DMT is "presumably inactivated through metabolic deamination and hence must be administered parentally or with some amine oxidase inhibitor." Cozzi (2009) (**GX15** at 49) explains DMT causes an intense dream-like state with colorful visual illusions.

Report, **GX11**) does not mean that 5-MeO-MiPT is 15-times *stronger* than DMT. As discussed above, 5-MeO-MiPT and DMT have entirely different profiles.

I certify under penalty of perjury that the foregoing is true and correct.

Executed on 7/14/22

DocuSigned by:
Dillan DiNardo
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