UNITED STATES DEPARTMENT OF JUSTICE

Drug Enforcement Administration

In the Matter of **Schedules of Controlled Substances: Placement of 2,5-dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-chloroamphetamine (DOC) in Schedule I**	**Docket No. 24-24**

ORDER FOR PREHEARING STATEMENTS

On December 13, 2023, the Drug Enforcement Administration ("DEA") published a Notice of Proposed Rulemaking with docket number DEA1156[1] and titled "Schedules of Controlled Substances: Placement of 2,5-dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-chloroamphetamine (DOC) in Schedule I" ("Notice of Proposed Rulemaking" or "NPRM"). 88 Fed. Reg. 86,278 (2023). The Notice of Proposed Rulemaking provided a January 12, 2024 deadline for requests for a hearing.[2] *Id*. at 86,278-79. The Notice of Proposed Rulemaking further states that "[i]n accordance with 21 U.S.C. 811 and 812, the purpose of a hearing would be to determine whether DOI and/or DOC meet the statutory criteria for placement in schedule I, as proposed in this rule." *Id.* at 86,280.

On January 8, 2024, Panacea Plant Sciences ("Panacea"), acting *pro se*,[3] filed a Request for Hearing ("Panacea RFH"),[4] regarding the proposed placement of DOI and DOC in Schedule

[1] For purposes of these administrative proceedings, all filings shall be captioned as shown above with the Matter title and Docket No. 24-24. Additionally, due to the number of parties involved in this matter, the parties are further directed to include in the title of their pleadings the filing party's name (e.g., "XYZ Company's Prehearing Statement"). If the filing is a joint pleading, it should be designated as such.

[2] The NPRM states specifically that "[r]equests for a hearing . . . must be received or postmarked on or before January 12, 2024." 88 Fed. Reg. 86,278, 86,278-79.

[3] In accordance with 21 C.F.R. § 1316.50, which is made applicable to the instant proceeding pursuant to 21 C.F.R. § 1308.41, Panacea is advised of its right to seek representation by a qualified attorney at its own expense. Representation options should be explored and finalized as expeditiously as possible.

[4] A copy of Panacea's RFH is provided as Attachment A.

I of the Controlled Substances Act. In its filing, Panacea specifically requests a hearing. Panacea RFH at 1. Panacea's RFH (1) sets forth its reasons why it opposes DEA's proposed action; (2) requests that the proposed rulemaking be withdrawn or subject to additional consultation prior to rulemaking; (3) contends that the DEA's rulemaking procedures subject it to unconstitutional administrative proceedings; and (4) provides comments and challenge to DEA's proposed action. *Id.* at 1-10.

On January 23, 2024,[5] the Science Policy Council, Students for Sensible Drug Policy ("SSDP"), acting *pro se*,[6] filed a Request for Hearing ("SSDP RFH"),[7] regarding the proposed placement of DOI and DOC in Schedule I of the Controlled Substances Act. In its filing, SSDP specifically requests a hearing. SSDP RFH at 1. SSDP opposes DEA's proposed scheduling of DOI and DOC, and requests that DEA "[m]aintain the current non-scheduled status of DOI and DOC to expedite research into 5-HT_2 receptors and their influence on disease states and chronic pain." *Id.* at 5.

On January 23, 2024,[8] Dr. Raul A. Ramos,[9] Amelia A. Furbish, PharmD, and Megan Francis, through counsel, filed a Request for Hearing ("Ramos, Furbish, & Francis RFH"),[10] regarding the proposed placement of DOI and DOC in Schedule I of the Controlled Substances Act. In their filing, Dr. Ramos, Ms. Furbish, and Ms. Francis specifically request a hearing. Ramos, Furbish, & Francis RFH at 1. They oppose DEA's proposed scheduling of DOI and DOC on the basis that they "believe that the scheduling of DOI and DOC would not protect the public from harm" in part because "these compounds are essential to scientific research." *Id.* at 3.

On March 28, 2024, DEA issued a Notice of Hearing on Proposed Rulemaking with Docket No. DEA1156 and titled "Schedules of Controlled Substances: Placement of 2,5-

[5] The SSDP RFH envelope does not bear a postmark, but contains other markings showing it was in the mail prior to January 12, 2024.
[6] In accordance with 21 C.F.R. § 1316.50, which is made applicable to the instant proceeding pursuant to 21 C.F.R. § 1308.41, SSDP is advised of its right to seek representation by a qualified attorney at its own expense. Representation options should be explored and finalized as expeditiously as possible.
[7] A copy of SSDP's RFH is provided as Attachment B.
[8] The Ramos, Furbish, & Francis RFH envelope is postmarked January 12, 2024.
[9] Dr. Raul A. Ramos also appears as a signatory on the SSDP RFH. *See* SSDP RFH at 6.
[10] A copy of the Ramos, Furbish, & Francis RFH is provided as Attachment C.

dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-chloroamphetamine (DOC) in Schedule I; Announcement of Hearing" ("Notice of Hearing"). The Notice of Hearing provides that "[u]pon review of the requests for hearing, [the Administrator has] authorized a hearing, and direct[s] the Chief Administrative Law Judge to assign the matter to an Administrative Law Judge who will complete all prehearing procedures, conduct a due process hearing in accordance with the Administrative Procedure Act (5 U.S.C. 551-559), the CSA (21 U.S.C. § 811, *et seq*), and the DEA regulations, and issue a recommended decision for the Agency's review and action." Notice of Hearing at 2.

On April 1, 2024, the Chief Administrative Law Judge issued an Order Assigning Administrative Law Judge ("Assignment Order"), assigning me to preside over this matter. Assignment Order at 1.

Upon consideration of each request for hearing, it is hereby **ORDERED** that, given the importance that parties have standing to participate in these proceedings, any motions related to whether a party satisfies the applicable standing requirements and satisfies the regulatory definition of "interested person"[11] be filed[12] no later than **2:00 p.m. Eastern Time ("ET")** on **April 17, 2024**. Any responsive filings to such filed motions will be due by **2:00 p.m. ET** on **April 24, 2024**.

It is further **ORDERED** that the Government, no later than **2:00 p.m. ET** on **April 17, 2024**, file and serve on each party requesting a hearing (collectively, the "Petitioners") a prehearing statement. It is further **ORDERED** that each of the Petitioners, no later than **2:00 p.m. ET** on **May 1, 2024**, file and serve on the Government and on the other Petitioners a prehearing statement.

The Government's and the Petitioners' prehearing statements must contain the following sections:

1. **Issue(s).** Statement of the perceived issues.
2. **Requested Relief.** Statement of the relief requested.

[11] 21 C.F.R. § 1300.01.

[12] Absent advance leave by this tribunal on a motion supported by good cause, filed documents (other than noticed proposed exhibits offered by a party on the merits) shall be limited to fifty (50) pages each (utilizing 12-point characters and 1-inch margins). All filed documents shall be **signed** (electronic signatures acceptable) by the person filing the document and the **pages shall be numbered**.

3. **Stipulations.** Proposed stipulations and admissions of fact. Each party is directed to examine available evidence and determine which facts may be the subject of stipulation to narrow the issues to those that will be and should be the subject of contested litigation.

4. **Witnesses.** Names and *current* addresses of all witnesses whose testimony is to be presented. The Petitioners should note that if a member of the Petitioners, or a representative thereof, intends to testify, that person must be listed as a witness, and a summary of his or her testimony as described below must be provided.

5. **Summary of testimony.** Summary of the testimony of each witness. The summaries are to state what the testimony will be, rather than merely list the areas to be covered. The parties are reminded that testimony not disclosed in the prehearing statements or pursuant to subsequent rulings is likely to be excluded at the hearing.

6. **Documents.** A list of all documentary evidence, including affidavits and other exhibits to be offered in evidence, specifying the number of pages in each. Each exhibit is to be numbered or lettered ("For Identification") with the designation to be used at the hearing.

7. **Position regarding hearing situs.** Statement of position regarding the location where the hearing will be conducted. Although the regulations direct that the hearing take place at the time and place designated by the Notice of Hearing,[13] the parties may raise issues relative to logistics that militate in favor of a different location.[14]

8. **Other matters.** Any other matters that the parties consider relevant.

9. **Best estimate as to time required for presentation of own case.**

It is further **ORDERED** that **a prehearing conference ("PHC") in this matter will be conducted by video teleconference ("VTC")**[15] on **May 3, 2024, at 12:00 noon ET**;[16] and it is

[13] 21 C.F.R. § 1301.45.

[14] In the discretion of the tribunal, some or all portions of these proceedings may be conducted through the use of video-teleconference ("VTC") technology.

[15] Logistical issues (including party availability) will be coordinated by Law Clerk T.J. Gleason, who can be reached by telephone at (571) 362-8683 or via email at Timothy.J.Gleason@dea.gov. To access the VTC PHC, the respective parties will receive an evite to the email addresses of record in this case. Parties may also attend the PHC in-person by notifying the Law Clerk no later than one day prior to the PHC.

[16] The Notice of Hearing provides that "the hearing will commence on June 10, 2024, at 9 a.m. ET at the DEA Hearing Facility, 700 Army Navy Drive, Arlington, VA 22202." Notice of Hearing at 2. In accordance with the Notice of Hearing, the tribunal will conduct prehearing proceedings on a timeframe such that this hearing will commence on June 10, 2024. However, in the unlikely event that a continuance of the hearing date becomes necessary, the parties must be prepared with dates of availability for their respective witnesses at least three months out from the prehearing conference date. As stated in the Notice of Hearing, "[t]he hearing . . . may be continued from day to day or recessed to a later date without notice other than announcement thereof by the Administrative Law Judge at the hearing." *Id.* at 1, 2-3.

further **ORDERED** that all proceedings will be governed by the provisions of 21 C.F.R. §§ 1316.41-1316.68.[17] Your attention is specifically directed to 21 C.F.R. § 1316.45, which provides, *inter alia*, that "[d]ocuments shall be dated and deemed filed upon receipt by the Hearing Clerk."[18] Only one method from the following document filing options may be utilized.

Electronic Filing: The preferred method of filing correspondence in these proceedings is as a PDF attachment via email to the DEA Judicial Mailbox (**ECF-DEA@dea.gov**). The forwarding email on all electronically-filed correspondence must indicate that it was simultaneously served on all other parties via email. All Petitioners must ensure that all documents filed with the DEA Judicial Mailbox are simultaneously served on the Government Mailbox (**dea.registration.litigation@dea.gov**) and on all other Petitioners and include a Certificate of Service at the end of the filed document. Any request(s) to modify email addresses of a party or counsel must be made on notice to this tribunal and all other parties. The email receipt date reflected by the DEA Judicial Mailbox server shall conclusively control all issues related to the date of service of all filed correspondence, provided however, that correspondence received after 5:00 p.m., local Washington, D.C. time, will be deemed to have been received on the following business day. ***Note: While email is utilized as the method to forward documents for filing—as attachments—no substantive matter communicated through the body of a forwarding email will be considered***. The parties are directed to refrain from including social security numbers or personally identifiable information in electronically-filed documents. ***Proposed exhibits will not be accepted via electronic filing***.

Hard Copy Filing: Alternatively, correspondence may be filed in hard-copy form. Hard-copy filings must be served in triplicate and addressed to my attention at: **DEA Office of Administrative Law Judges, 8701 Morrissette Drive, Springfield, VA 22152**. Because the DEA Hearing Facility is not physically collocated with the DEA mailing address, ***hard copy filings must be posted sufficiently in advance of the due date to assure timely receipt by this office***.

Failure to timely file a prehearing statement that complies with the directions provided

[17] Additional helpful information regarding DEA administrative proceedings may be found at the OALJ website, https://www.dea.gov/administrative-law-judges.

[18] The parties are cautioned to ensure that all filings are made timely by the 2:00 p.m. Eastern Time ("ET") filing deadline.

above may result in a sanction, including (but not limited to) a waiver of hearing and an implied withdrawal of a request for hearing. Prehearing statements should not include motions, which should be filed separately.[19]

It is further **ORDERED** that any requests for extension of time to file must be made by written motion sufficiently in advance of scheduled deadlines to be considered and ruled upon.[20]

Dated: April 2, 2024

PAUL SOEFFING
Digitally signed by PAUL SOEFFING
Date: 2024.04.02 15:25:43 -04'00'

PAUL E. SOEFFING
U.S. Administrative Law Judge

CERTIFICATE OF SERVICE

This is to certify that the undersigned, on April 2, 2024, caused a copy of the foregoing to be delivered to the following recipients: (1) Paul A. Dean, Esq., Counsel for the Government, via email at Paul.A.Dean@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) Science Policy Council, Students for Sensible Drug Policy C/O Elijah Zorro Ullman, via email at ezu123@gmail.com; and (4) Robert T. Rush, Esq., via email at rrush@rrushlaw.com.

TAYONNA EUBANKS (Affiliate)
Digitally signed by TAYONNA EUBANKS (Affiliate)
Date: 2024.04.02 15:29:26 -04'00'

Tayonna A. Eubanks
Secretary (CTR)
Office of Administrative Law Judges

[19] A prehearing ruling setting deadlines will be issued after the prehearing conference.
[20] Filing deadlines are adhered to strictly. In the event a document is filed untimely, without an approved extension of time granted in advance by this tribunal, the untimely filing must include a separate Motion for Leave to file the untimely document and such Motion for Leave must include a statement of good cause for the late filing. Documents that are submitted for filing untimely will be accepted for filing at the discretion of the tribunal if good cause is shown.

January 2, 2024

Drug Enforcement Administration, Attn: Hearing Clerk / OALJ

8701 Morissette Dr.

Springfield VA 22152

Subject: Request for Hearing

Dear Sir:

The undersigned Panacea Plant Sciences C/O David Heldreth hereby requests a hearing in the matter of: the Placement of 2,5-dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-chloroamphetamine (DOC) in Schedule I also identified as Docket No. DEA1156.

(1) state with particularity the interest of the person in the proceeding; (2) state with particularity the objections or issues concerning which the person desires to be heard; and (3) state briefly the position of the person with regarding to the objections or issues.

Panacea Plant Sciences would like to verify standing in the rule making by asserting that our company:

1.) is currently not licensed by the DEA.
2.) has research, IP and patent filings which incorporate DOI and DOC.
3.) will be harmed via increased oversight, expenses, etc from this unnecessary rule making which would require the company to secure a new license/permit from the DEA.

Now in regards to the current rule making, let us begin:

A) To start there are apparent errors in the rulemaking process, in that the DEA did not consult with tribal governments as required under Executive Order 13175.

The rulemaking references active Executive Order 13175 - Consultation and Coordination with Indian Tribal Governments – however, it asserts that no such consultation with tribal governments is necessary, or as stated directly below:

"This proposed rule does not have tribal implications warranting the application of It does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal Government and Indian tribes, or on the distribution of power and responsibilities between the Federal Government and Indian tribes."

This statement is incorrect as this rulemaking will change the status of a substance under federal law to Schedule 1 which will then as such require tribal law enforcement to enforce this new law as reservations are regulated as federal lands and many tribal law codes reference federal law and

Attachment A
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the Controlled Substances Act. As such the current rulemaking will create a situation in which tribal governments and law enforcement will be required to train law enforcement on the new laws and this alone will impose direct costs on tribal entities and governments. Additionally, the costs of any enforcement of these new laws incurred from arrests, testing, jailing, etc. which falls on tribal governments again represent burdens and reasons for the DEA/Department of Justice to conduct a tribal consultation prior to rulemaking as is required under EO 13175. From the text:

"To the extent practicable and permitted by law, no agency shall promulgate any regulation that has tribal implications, that imposes substantial direct compliance costs on Indian tribal governments, and that is not required by statute, unless:

(1) funds necessary to pay the direct costs incurred by the Indian tribal government or the tribe in complying with the regulation are provided by the Federal Government; or

(2) the agency, prior to the formal promulgation of the regulation,

(A) consulted with tribal officials early in the process of developing the proposed regulation;

(B) in a separately identified portion of the preamble to the regulation as it is to be issued in the ***Federal Register*** *, provides to the Director of OMB a tribal summary impact statement, which consists of a description of the extent of the agency's prior consultation with tribal officials, a summary of the nature of their concerns and the agency's position supporting the need to issue the regulation, and a statement of the extent to which the concerns of tribal officials have been met; and*

(C) makes available to the Director of OMB any written communications submitted to the agency by tribal officials."

Additionally, under the current DOJ tribal consultation policy, the DEA and DOJ are tasked to not narrowly define when it is necessary to consult tribal governments, but to do so in a way that is widely encompassing and to err on the side of consulting, rather than not. From the DOJ's own tribal consultation policy:

"The requirements of Executive Order 13175 and this Policy Statement generally will be construed liberally in favor of Consultation on any given policy as defined above with Tribal implications. Consultations may be organized in a variety of ways, from a single group discussion to a more iterative process involving a series of discussions. All decisions regarding whether and how to conduct a Consultation, or whether a given policy or topic has Tribal implications, will be coordinated with the Department's Office of Tribal Justice."

A Freedom of Information request has been filed to determine if this step was taken and if the DEA and DOJ, prior to rulemaking, actually sent this policy to the DOJ Office of Tribal Justice for a determination.

Meanwhile, actions by the USPTO show the current administration is aware of the burden of EO 13175 and is conducting a tribal consultation which will be held in January:

Perhaps the DEA can contact the USPTO for guidance on how to conduct such a consultation.

There are 574 federally recognized tribes and around *258 tribal law enforcement agencies.* That is a large amount of affected tribal entities and a large impact. As such I ask that the DEA withdraw the current rulemaking and begin the mandated tribal consultation process under EO 13175 and DOJ's own policy. The DOJ policy also requires notice at least 30 days before the date of consultation.

As such Panacea Plant Sciences requests the rulemaking at hand be:

1. Withdrawn; and either
2. No further action on DOI or DOC scheduling by DEA; or
3. Conduct tribal consultation which begins with a publication of notice seeking tribal input before rulemaking.

B) The next issue at hand that must be dealt with is, the DEA's current rulemaking references the Regulatory Flexibility Act. However, the DEA finds that there is not a significant impact on small entities.

From the text of the rulemaking:

"The Administrator of DEA, in accordance with the Regulatory Flexibility Act, , has reviewed this proposed rule, and by approving it, certifies that it will not have a significant economic impact on a substantial number of small entities.

DEA proposes placing the substances DOI and DOC (chemical names: 2,5-dimethoxy-4-iodoamphetamine [DOI] and 2,5-dimethoxy-4-chloroamphetamine [DOC]), including their salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation, in schedule I of the CSA. This action is being taken, in part, to enable the United States to meet its obligations under the 1971 Convention for DOC. If finalized, this action would impose the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances on persons who handle (manufacture, distribute, reverse distribute, import, export, engage in research, conduct instructional activities or chemical analysis with, or possess), or propose to handle DOI and DOC.

According to HHS, and also by DEA's findings in this proposed rule, DOI and DOC have a high potential for abuse, have no currently accepted medical use in treatment in the United States, and lack accepted safety for use under medical supervision. There appear to be no legitimate sources for DOI and DOC as marketed drugs in the United States, but DEA notes that these substances are available for purchase from legitimate suppliers for scientific research. There is

no evidence of significant diversion of DOI and DOC from legitimate suppliers. As such, the proposed rule, if finalized, is not expected to result in a significant economic impact on a substantial number of small entities."

We find fault with the DEA assessment that there will not be a substantial impact on small businesses and small entities from this rule-making. Panacea Plant Sciences itself is a small business which qualifies under the Regulatory Flexibility Act to have consultation. Currently, the compounds DOI and DOC are not contained in any federal drug schedule and as such are unregulated essentially. As such there are not any regulations that would require a small business or other small entity to disclose that they are utilizing DOI and DOC for research or for any other business development. Due to this, I am unsure how the DEA measured or even attempted to measure the impact to small business. Additionally, I wonder if this rule was shared with the Small Business Administration to ascertain any possible impacts or from my understanding it wasn't and the DEA administrator made a convenient finding that would allow her to move forward without following the requirements of the Regulatory Flexibility Act.

The Regulatory Flexibility Act allows this, but also as it says below requires the administrator to provide such certification and statement to the Chief Counsel for Advocacy of the Small Business Administration. We are curious if this step was done as the rule making does NOT mention. We have sent a FOIA request to ascertain if this requirement was fulfilled.

"(b) Sections 603 and 604 of this title shall not apply to any proposed or final rule if the head of the agency certifies that the rule will not, if promulgated, have a significant economic impact on a substantial number of small entities. If the head of the agency makes a certification under the preceding sentence, the agency shall publish such certification in the Federal Register at the time of publication of general notice of proposed rulemaking for the rule or at the time of publication of the final rule, along with a statement providing the factual basis for such certification. The agency shall provide such certification and statement to the Chief Counsel for Advocacy of the Small Business Administration."

"*If finalized, this action would impose the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances on persons who handle (manufacture, distribute, reverse distribute, import, export, engage in research, conduct instructional activities or chemical analysis with, or possess), or propose to handle DOI and DOC."*

The DEA provides a wide scope of activity that will be impacted by this rule-making. DOI and DOC are widely used as standards for comparing the activity of a compound on the 5-HT2A receptor which is found in the human body and animals. This is because in order to validate the data you need to have a standard with which to calibrate and compare. The same principle occurs when using a known weight to calibrate a scale. DOI and DOC are also widely used in animal trials in which it is necessary to study the 5-HT2A system in animals or humans. Additionally, DOI and DOC have recently shown benefits for asthma, pain and inflammation in preliminary studies and follow-up studies are needed. All of this would be illegal without first obtaining a DEA license/permit if the DEA gets its way and finalizes this rulemaking. A DEA permit/license which costs thousands of dollars and requires thousands of dollars more in security and

regulatory costs. These regulatory costs and restrictions imposed by the current rulemaking will strangle and highly impact small business and other small entities.

There are roughly 4,000 universities that would qualify under the Regulatory Flexibility Act as small entities and each of those has hundreds or thousands of students who could be studying DOI or DOC or using them in research. In 2023 alone there were 178 studies using DOI and DOC found among scholarly journals on Google Scholar. That's 178 small entities. Additionally, there could be any number of small businesses, such as Panacea Plant Sciences throughout the U.S. We believe this high volume of use and high volume of impacted small entities and businesses is indicated by the volume of comments which the DEA has received on this rulemaking. As such the DEA is statutorily bound to follow the regulations of the Regulatory Flexibility Act.

From the Regulatory Flexibility Act:

"§ 602. Regulatory agenda

(a) During the months of October and April of each year, each agency shall publish in the Federal Register a regulatory flexibility agenda which shall contain —

(1) a brief description of the subject area of any rule which the agency expects to propose or promulgate which is likely to have a significant economic impact on a substantial number of small entities;

(2) a summary of the nature of any such rule under consideration for each subject area listed in the agenda pursuant to paragraph (1), the objectives and legal basis for the issuance of the rule, and an approximate schedule for completing action on any rule for which the agency has issued a general notice of proposed rulemaking, and

(3) the name and telephone number of an agency official knowledgeable concerning the items listed in paragraph (1).

(b) Each regulatory flexibility agenda shall be transmitted to the Chief Counsel for Advocacy of the Small Business Administration for comment, if any.

(c) Each agency shall endeavor to provide notice of each regulatory flexibility agenda to small entities or their representatives through direct notification or publication of the agenda in publications likely to be obtained by such small entities and shall invite comments upon each subject area on the agenda.

(d) Nothing in this section precludes an agency from considering or acting on any matter not included in a regulatory flexibility agenda, or requires an agency to consider or act on any matter listed in such agenda."

We would like to let it be known that this rulemaking was not included on the DOJ or DEA Regulatory Flexibility Agenda. We would like the rulemaking withdrawn until this can be done.

Additionally, we believe that under the Regulatory Flexibility Act requirements that the DEA does not need to conduct this rule making in order to achieve the goals it states while also not impacting small entities and businesses. Currently, under the Analog Act any compound which is substantially similar to a controlled substance may also be found illegal for human consumption and related uses. However, the use of that same substance is and would be legal if it were to be used for in vitro studies, cell studies, animal trials of related uses. That is the current status quo. Under the current state of things there is as the DEA states in their own 8-factor analysis no apparent illicit diversion of DOI and DOC. As such there is no danger or need for a regulatory change and the only way to reduce or prevent impact on small entities and business under the Regulatory Flexibility Act is to have this rulemaking withdrawn and not resubmitted.

As such Panacea Plant Sciences requests the rulemaking at hand be:

1. Withdrawn; and either
2. No further action on DOI or DOC scheduling by DEA; or
3. Small business and entity consultation which begins with a publication to that end prior to rulemaking in 2024 and potential final rulemaking in 2025.

C) The next issue at hand is that the DEA's attempted rulemaking seeks to subject Panacea Plant Sciences (and any other parties who may request a hearing to challenge the rulemaking) — to an unconstitutional administrative proceeding (the "Administrative Hearing") before a DEA Administrative Law Judge ("ALJ"). DEA issued a notice in the federal register on rule making entitled: "Placement of 2,5-dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-chloroamphetamine (DOC) in Schedule I." The DEA rulemaking requires an appearance before an ALJ from the agency in order to challenge the rulemaking which has the potential to irreparably harm Panacea Plant Sciences.

The DEA via its rulemaking seeks to compel Panacea Plant Sciences to participate in an unlawful adjudicative process before a DEA ALJ who was appointed in violation of the Appointments Clause of Article II, Section 2, of the Constitution and is not accountable to President, in violation of the Take Care Clause of Article II, Section 3 of the Constitution. Panacea Plant Sciences is entitled to injunctive and declaratory relief to prevent the irreparable harm it would suffer if subjected to such an unconstitutional proceeding.

The United States Supreme Court has found that an ALJ appointment process nearly identical to that used by DEA is unconstitutional. DEA, however, has done nothing to conform its ALJ appointment process to constitutional requirements. Moreover, statutory restrictions on an ALJ's removal violate the President's Article II executive power. DEA nonetheless seeks to compel Panacea Plant Sciences to participate in an unconstitutional DEA administrative proceeding. Panacea Plant Sciences seeks declaratory and injunctive relief to prevent the irreparable harm it would suffer if subjected to such an unconstitutional proceeding.

DEA ALJs are executive "officers" for purposes of Article II's Appointments Clause. They hold continuing positions, established by law, in which they exercise significant authority and discretion presiding over DEA administrative hearings and adjudicating adversarial enforcement proceedings.

Under the Appointments Clause, inferior Article II "officers" such as DEA's ALJs must be appointed either by the President or the Head of their Department, the Attorney General of the United States. U.S. Const. art. II, § 2, cl. 2. DEA ALJs, however, are appointed by neither.

On information and belief, the DEA ALJ who would preside over Panacea Plant Sciences' administrative hearing would be selected from a pool of candidates provided by the White House Office of Personnel Management ("OPM") and appointed by the DEA Administrator upon recommendation from DEA's Chief ALJ. (Pursuant to Federal Rule of Civil Procedure 11(b)(3), any allegations made on information and belief will have additional evidentiary support after a reasonable opportunity for further investigation on discovery. To be clear, however, with respect to ALJ appointments, DEA's website says simply that ALJs "are appointed for life under the Administrative Procedures Act . . . ." It makes no mention of whether ALJs are currently appointed by the Attorney General or an inferior officer. However, Panacea Plant Sciences' has reviewed the recent ongoing case of Ascent Pharmaceuticals in which the counsel were directed to Chambers for the information. An individual assigned to ALJ's Wallbaum's Chambers said simply, "we do not give out that information.")

In June 2018, the United States Supreme Court confirmed that this ALJ appointment process is unconstitutional in Lucia v. S.E.C., 138 S. Ct. 2044 (2018). Although the Court's decision specifically addressed the appointment of ALJs for the Securities and Exchange Commission ("SEC"), its reasoning equally applies to the appointment of DEA's ALJs. The Solicitor General explicitly acknowledged this fact in a memorandum addressed to all agency general counsels made public following the Supreme Court's decision in Lucia. In that memorandum, the Solicitor General stated that "SEC ALJs, and other ALJs who exercise similar powers, are inferior officers and must be appointed as such." (Office of the Solicitor General, Guidance on Administrative Law Judges after Lucia v. SEC (S. Ct.), (July 23, 2018) available at

The framework for removal of DEA's ALJs is similarly unconstitutional. Article II vests "[t]he executive Power" in the President, including the ultimate authority to remove officers to ensure that the law is "faithfully executed." U.S. Const. art. II, § 1, cl. 1; id. § 3. The Supreme Court has held that, because the executive power is vested in the President, Article II requires inferior officers, such as ALJs, to be answerable to the President, and not separated from the President by attenuated chains of accountability. See Free Enter. Fund v. Pub. Co. Acct. Oversight Bd., 561 U.S. 477, 492-98 (2010) ("Free Enterprise"). Statutory prohibitions found in Sections 7521(a) and 1202(d) of Title 5 of the United States Code prevent the President and Attorney General from removing DEA ALJs. Rather, they may be removed only for "good cause" as "determined" by the Merit Systems Protection Board ("MSPB"), whose members themselves can only be removed by the President on certain limited "good cause" grounds. This scheme—creating two layers of "for cause" protection between the President (or Attorney General) and his inferior

officer ALJs—deprives the President (or Attorney General) from exercising his executive oversight duties and therefore is violates Article II. Id. at 492.

Ascent Pharmaceuticals has filed a case against the DEA for similar grounds regarding the ALJ in New York federal court and a new case has just been filed in Texas federal court by Inmar RX Solutions Inc for the same reason. The DEA ALJ as currently stands are unconstitutional.

Panacea Plant Sciences requests this hearing, but due to the likely unconstitutional nature of the DEA ALJ, Panacea Plant Sciences requests the rulemaking at hand be:

1. Withdrawn; or delayed until there are constitutionally appointed ALJ and constitutionally corrected ALJ removal processes at the DEA which allow the hearing to take place legally and constitutionally.

D) Panacea Plant Sciences comments and challenge to the current rulemaking entitled "Placement of 2,5-dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-chloroamphetamine (DOC) in Schedule I" will be expressed in full below, but in the essential form are that this rule making is a superfluous and unnecessary action as these items are not a public danger or item of concern, and that additionally any attempt to control these items will damage the ability to conduct scientific research on the human body, brain, mental health, pharmacology; and will potentially reduce access for research on the use of these items themselves as therapeutic compounds.

Panacea Plant Sciences finds fault with the DEA 8-factor analysis. There is no case for scheduling DOI or DOC.

1. **Its actual or relative potential for abuse;**
   DOI and DOC are not addictive compounds and have not been shown to have addictive or to create dependence. There is no case showing DOI or DOC alone carries a risk necessitating a listing on Schedule 1.

2. **Scientific evidence of its pharmacological effect, if known;**
   The DEA is using anecdotal evidence from an online website called Erowid of people claiming to use DOI and DOC online as evidence of a pattern of use. The DEA's own analysis admits that there is no evidence that any of the users actually used these substances or even that any of the entries are of real people who actually took any substance.

   From the DEA 8 factor analysis:
   "...However, it is impossible to know whether street drugs sold to an individual as "DOI" or "DOC" are actually the substances they are purported to be in the absence of a chemical analysis or evaluation of biological fluids following ingestion."

3. **The state of current scientific knowledge regarding the drug or other substance;**
   Under this section the DEA states that:
   "Medical Use of DOI and DOC

DOI and DOC are not available in approved human drug products in the United States or in any other country and no data are available on their medical use in the treatment of any condition."

The agency stops there and does not delve into the recent research which is being conducted on DOI and DOC which show medical applications and potential use as treatments for a variety of conditions. 178 studies were published on Google Scholar which referenced these compounds in 2023 alone. Research on DOI and DOC include data showing it has ability to treat: asthma, and addiction for example.

5-HT2 receptor activation alleviates airway inflammation and structural remodeling in a chronic mouse asthma model

R-(-)2,5-dimethoxy-4-iodoamphetamine [(-)-DOI] decreases cocaine demand in a 5-HT2AR-mediated -
manner

4. **Its history and current pattern of abuse;**
The DEA is using anecdotal evidence from an online website called Erowid of people claiming to use DOI and DOC online as evidence of a pattern of use. The DEA's own analysis admits that there is no evidence that any of the users actually used these substances or even that any of the entries are of real people who actually took any substance.

From the DEA 8 factor analysis:
"...However, it is impossible to know whether street drugs sold to an individual as "DOI" or "DOC" are actually the substances they are purported to be in the absence of a chemical analysis or evaluation of biological fluids following ingestion."

We find that there is little to no evidence of a pattern of use of these compounds by the general public. There is no case showing DOI or DOC alone carries a risk necessitating a listing on Schedule 1.

5. **The scope, duration, and significance of abuse;**
For DOI there was only an average of 3 findings a year approximately. Additionally, was that finding of an illegal use? Or was the compound potentially being used for research in some way which would be legal under the analog act? That is unknown. There is no case showing DOI or DOC alone carries a risk necessitating a listing on Schedule 1.

6. **What, if any, risk there is to the public health;**
The DEA admits no deaths in relation to DOI are known and refers to 3 incidents with DOC. However, in two of these there was known prior drug use, whether at the time or in

the patients past of opiates and amphetamines. These items are much more likely to be connected to the deaths. Additionally, the third case involves the taking of large doses of DOC and in combination again with other drugs. Combinations of even legal compounds can carry risks. There is no case showing DOI or DOC alone carries a risk necessitating a listing on Schedule 1.

7. **Its psychic or physiological dependence liability;**
   DOI and DOC are not addictive compounds and have not been shown to have addictive natures or to create dependence. There is no case showing DOI or DOC alone carries a risk necessitating a listing on Schedule 1.

8. **And, Whether the substance is an immediate precursor of a substance already controlled under the CSA?**
   DOI and DOC are not precursors of other items in the CSA.

Further evidence and information will be presented in the future.

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

Panacea Plant Sciences

C/O David Heldreth

14321 Se 49th St

Bellevue WA 98006

Respectfully yours,

David Heldreth

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1.4.24

Drug Enforcement Administration, Attn: Hearing Clerk/OALJ

Subject: Request for Hearing, § 1316.47, Docket No.1156

To whom it may concern,

The undersigned, Tanner L. Anderson, Anousheh Bakhti-Suroosh, Devin P. Effinger, PhD, Tyler G. Ekins, PhD, Christopher W. Fields, Joseph J. Hennnessey, Alaina M. Jaster, PhD, Raul A. Ramos, PhD, Elijah Z. Ullman, hereby requests a hearing in the matter of: **Schedules of Controlled Substances: Placement of 2,5-dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-chloroamphetamine (DOC) in Schedule I,** ***Docket No. 1156***

(A) (State with particularity the interest of the person in the proceeding.)

See attached document

(B) (State with particularity the objections or issues, if any, concerning which the person desires to be heard.)

See attached document

(C) (State briefly the position of the person with regard to the particular objections or issues.)

See attached document

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

Elijah Z. Ullman

1263 Poinset Pl, Decatur GA, 30033

Respectfully yours,

Elijah Z. Ullman

PhD Candidate in Molecular and Systems Pharmacology | Emory University

Chair, Science Policy Council, Students for Sensible Drug Policy

Attachment B
Docket No. 24-24

For the Purpose of § 1316.47 *Request for Hearing Regarding Docket No.1156*

On behalf of the Science Policy Council, Students for Sensible Drug Policy
C/O Elijah Zorro Ullman

Docket No. DEA1156

On the proposed Schedule 1 classification of 2,5-dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-chloroamphetamine (DOC)

The below signatories are interested persons in the Request for Hearing on DEA1156, and have standing for a hearing on this matter as they are scientists utilising or have utilised DOI in their research.

Executive Summary

Psychedelic drugs such as psilocybin have experienced a marked increase in media and scientific attention within the last decade for potential treatment of psychiatric disorders such as post-traumatic stress disorder (PTSD), anxiety, obsessive-compulsive disorder (OCD), treatment-resistant depression and substance use disorders (Bogenschutz et al., 2022; Johnson et al., 2017; Sanders, 2021; Tullis, 2021; Vargas et al., 2021). Yet, many of these psychedelics act through a wide variety of receptor systems, and the exact identity, localization, and downstream mechanisms of the molecular targets that account for their therapeutic efficacy is an active area of research. DOI and DOC are invaluable research tools to study these receptor systems and their roles in therapeutic effects because, unlike more conventional psychedelic drugs such as psilocybin, DOI and DOC are highly selective for serotonin 2 receptors (5-HT_2). Activity at these receptors is thought to be the primary mechanism underlying subjective psychedelic drug effects as well as therapeutic benefit in clinical studies of psychiatric disease (Jaster & González-Maeso, 2023; Ling et al., 2022). Importantly, psychedelics are among the least harmful and least likely to be abused of all recreational drugs, considering their sporadic use patterns, non-reinforcing effects and rapid tolerance to the hallucinations and subjective effects (de la Fuente Revenga et al., 2022; Fantegrossi et al., 2004). Their low abuse potential paired with their clear medical benefits in clinical trials calls into question the legitimacy of their current Schedule 1 status (Nutt et al., 2020). The undersigned therefore asks for no changes in the scheduling of DOI and DOC due to their importance in serotonin and psychedelic pharmacology. We also Request a Hearing on this matter pursuant to 21 CFR 1316.47 as *Interested Persons.* Placement of DOI and DOC in Schedule 1 of the CSA is not commensurate with its abuse potential, and is further complicated by its extensive utility in scientific research as detailed below.

Interest of Petitioners

Placement of DOI and DOC in Schedule 1 of the CSA will cause irreparable harm to the research endeavours of the Undersigned; Placement in Schedule 1 will prevent the Undersigned from conducting their research. The Undersigned have significant expertise in behavioural and molecular models of addiction and characterization of the ensuing biochemistry and pharmacology. See the below Biographies for further information.

Actual or Relative Abuse Potential

Psychedelics have long been characterised for their unusual effects on sensory perception and subjective experiences. Until the last ten years, psychedelics have not been fully investigated utilising modern methodology or institutional review board regulations for their own use liability or ability to reduce drug use in both clinical and preclinical models.

While the Controlled Substances Act uses drug discrimination as an *in vivo* test to assess drug use liability in comparison to known "drugs of abuse", the core of drug discrimination is to evaluate the stimulus similarity between a test novel chemical entity and a reference agent. While psychedelics like DOI and DOC do substitute for DOM, LSD and psilocybin, this is due to their shared pharmacology at the 5-HT_2 receptors

(Glennon et al., 1982). As DOI and DOC's duration is approximately 36 hours in humans, the potential for abuse is minimal, as exemplified by relative lack of seizures of the compounds by law enforcement. In recent years, other measures that are more widely accepted tests of drug use include self-administration, intracranial self-stimulation and food versus drug choice operant responding (Spanagel, 2017). *In these more rigorous measures, DOI and some analogs have been shown to be non-reinforcing and to reduce reinforcing effects of other drugs*. Due to their long duration of action of 24+ h, much longer than other serotonergic psychedelics like LSD, they are less likely to be abused - as evidenced by the statistics). Law enforcement seizures have been exceptionally minimal (Drug Enforcement Administration, 2023b). It follows that compounds that are non-reinforcing, are generally non-addictive.

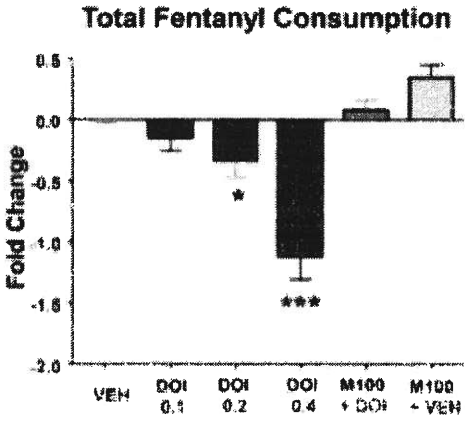

Figure 1. Decrease in fentanyl consumption shown as Log2 fold-change for each drug condition relative to the log-average of all vehicle sessions. Martin, 2021. Effects of 5-HT2A Receptor Stimulation on Economic Demand for Fentanyl after Intermittent and Continuous Access Self-Administration in Male Rats. *Addiction Biology*, 2021;26(3).

For example, DOM decreased heroin self-administration in non-human primates but did not alter food responding (Maguire, 2023). Similarly, DOI depressed intracranial self-stimulation in rats, which is in contrast to other drugs like heroin, cocaine and amphetamines, which typically stimulate responding (Jaster et al., 2022), and DOI was found to decrease ethanol preference in a conditioned place preference and two-bottle choice model (Oppong-Damoah et al., 2019). Most profoundly, DOI was found to dose-dependently decrease motivation for fentanyl seeking and decrease low-cost and total fentanyl consumption, which was evidenced to be dependent on 5-HT_{2A} activation (**Fig. 1** taken from (Martin et al., 2021). DOI was also found to accelerate natural extinction of opioid preference using a mouse conditioned place preference model (Jaster et al., 2024, unpublished).

To this end, if the same logic is applied to drug discrimination, all of these compounds may produce non-reinforcing effects and potentially attenuate use of other substances and therefore do not fall into the "high potential for abuse" category. With this consideration, the proposed reclassification of DOI and DOC into Schedule I of the CSA would be inappropriate solely based on the lack of indication for "high potential for abuse" and no "medicinal value," as there is a growing body of evidence that contradicts this opinion.

Importance as a Scientific Tool and Impact of Schedule 1 Classification

Because commonly used psychedelics like psilocybin and LSD had been classified as Schedule 1 drugs in 1970, DOI and DOC have represented legal and accessible research chemical alternatives to working with traditional psychedelics that had been widely used for "psycholytic therapy" in the 1960s.

DOI in particular, and phenethylamines like DOC in general, are extremely useful compounds for scientific research because they are highly selective agonists for 5-HT receptors over other closely related G-protein coupled receptors (Halberstadt et al., 2009, 2013). Specifically, DOI is especially important as a research chemical due to its high selectivity for the 5-HT_2 class of 5-HT receptors, including the 5-HT_{2A} receptor, which is known to be critical for the therapeutic effects of psychedelics (Cameron et al., 2021). As polypharmacology — the affinity of a compound for multiple receptors — complicates scientific study of the receptor of interest, the availability of DOI and related phenethylamines for scientific research is paramount.

Since 2012, DOI has been utilised in approximately 1,200 research articles in leading journals such as Cell, Nature, and Science. This number has only grown in the last two years. Scientists have gravitated towards DOI and DOC as benchmark compounds in pharmacotherapy research for diseases of the central and peripheral nervous systems due to its relative ease of accessibility and exceptional pharmacological profile. For example, a significant research effort has been undertaken to understand the crucial role of serotonin in the neuro-immune interactions that govern pain (Loyd et al., 2013; Richardson, 1990). In order to understand the role of the 5-HT_{2A} receptor in neuropathic pain, DOI has been used for behavioural, electrophysiological, cellular, and molecular experiments (Abbott et al., 1996; Kjørsvik Bertelsen et al., 2003; Rahman et al., 2011; Tokunaga et al., 1998). Further, DOI and its phenylethylamine analogs are being studied for chronic pain and as anti-inflammatory agents (Nichols, 2022), making them an important tool to understand and develop better and less addictive pain medications than opioids. Most recently, $1.5 million was granted by the Howard Hughes Medical Institute in 2023 to specifically study the effects of DOI on peripheral pain neurons.

The proposed Schedule 1 classification of DOI and DOC significantly reduces their accessibility as research chemicals for basic science research which is essential for novel drug development and understanding of conditions like pain, substance use and neuropsychiatric diseases. While laboratories may apply for a Schedule 1 DEA Licence, it is well understood amongst the scientific community that the financial barriers and bureaucratic red tape associated with obtaining a Schedule 1 licence and conducting research with these compounds amounts to a nearly prohibitive roadblock for many laboratories (Andreae et al., 2016; Henningfield et al., 2022). As such, many laboratories - including many of the Undersigned - may simply choose not to apply for a Schedule 1 Licence, and abandon projects within this sector. Thus, the proposed reclassification of DOI and DOC will significantly hamper and deter medical research, and delay the development of future pharmacotherapeutics for treating a variety of neuropsychiatric, substance use and inflammatory disorders. All of this promising research relies on complete characterization of the function of 5-HT_2 receptors.

Danger to Self and Public Health

According to the DEA, in the 19 years since these two compounds were first encountered by law enforcement in the U.S. there have only been *three* fatal complications associated with the use of DOC and *zero* involving DOI (Drug Enforcement Administration, 2023a). These numbers pale in comparison to lives claimed by opioids, which are typically Schedule 2 compounds that killed 47,000 Americans by overdose in 2018 alone (Chandler et al., 2020). In one case report in which DOC was attributed to death included the use of other compounds - the presence of DOC was negligible (< 10 ng/mL in cardiac blood sample) - but buprenorphine, cocaine and cannabis metabolites were also present complicating the cause of death (Lelievre et al., 2022).

There is ample scientific literature describing the fact that, on their own, many psychedelics have no known lethal dose and have minimal physiological toxicity. For commonly-used psychedelics like psilocybin and LSD, only a handful of overdose cases not involving other drugs have been documented, and their lethal doses have been estimated to be at least *one-thousand times* a standard dose (Gable, 2004). Other known physiological side effects of psychedelics, including acute autonomic effects, pulse and breathing irregularities, and headaches are relatively mild and often do not pose major health risks to the individual (Johnson et al., 2018). Although less is known about the possible toxicity associated with DOI and DOC, it is reasonable to assume they share similar properties as more commonly-used psychedelics like psilocybin and LSD, as they share similar pharmacological profiles. It is therefore, in our opinion, safe to assume that there is little concern for physiological toxicity or lethal outcomes with DOI and DOC.

Conclusion

Activation of the 5-HT_2 receptors is a common mechanism of action for all serotonergic psychedelic drugs and is likely necessary for their profound emotional, cognitive, and sensory effects, as well as their therapeutic effects. The significant effects of psychedelics on end-of-life anxiety, treatment-resistant depression, and substance use disorders have been extensively reported upon in the scientific literature in both humans and preclinical models (Davis et al., 2021; Griffiths et al., 2016; Jaster & González-Maeso, 2023; Tullis, 2021). See **Fig. 2** taken from Tullis et al., 2021.

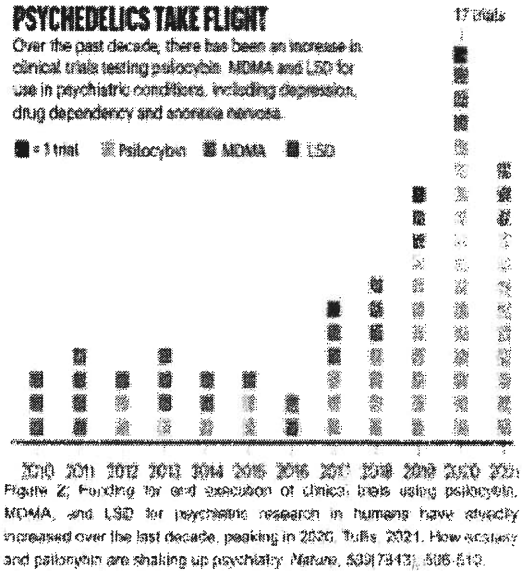

Figure 2: Funding for and execution of clinical trials using psilocybin, MDMA, and LSD for psychiatric research in humans have steadily increased over the last decade, peaking in 2020. Tullis, 2021. How ecstasy and psilocybin are shaking up psychiatry. *Nature*, 599(7883), 506-510.

Research using DOI and DOC is ongoing in a variety of fields that have a large impact on health. Both published and unpublished work with DOI has demonstrated its own potential utility in treatment of substance use disorders, including alcohol and opioid use (Oppong-Damoah et al., 2019; Jaster et al., 2024, unpublished). Restriction of access to these compounds within the research setting will hamper the ability to further study the utility of DOI and other psychedelics for these indications.

The process to obtain a Schedule 1 licence is long, arduous, and burdensome for laboratories that want to work with such substances. Due to DOI and DOC's value to scientific research and relative lack of abuse, it does not follow scientific or logical reasoning to place it into the Schedule 1 category. It is our opinion that it is morally wrong to impede the efforts of scientists working to develop therapeutics that could prevent suicide, eliminate PSTD in combat veterans, break the cycle of drug addiction, and alleviate intrusive thoughts and compulsive symptoms in patients with conditions that do not respond to currently available drugs (Sellers & Leiderman, 2018).

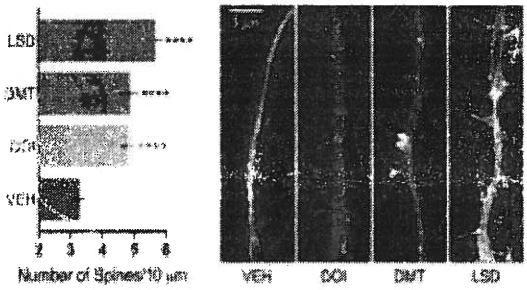

Figure 3: DOI and classic psychedelics like DMT and LSD swiftly promote the growth of dendritic spines, possibly acting as plastogens to exert their rapid therapeutic effects in animal models of psychiatric disease. Ly et al., 2018. Psychedelics promote structural and functional neural plasticity. Cell reports, 23(11), 3170-3182.

Lastly, classical and non-classical psychedelics like psilocybin and MDMA respectively, are coming down the FDA regulatory pipeline and these drugs will soon enter the consumer marketplace (Center for Drug Evaluation and Research, 2023; MAPS PBC, 2023). This resurgence in interest in psychedelic therapy is in no small part due to the data generated from basic science research using phenethylamines such as DOI to elucidate 5HT_2 receptor pharmacology and actions on structural and synaptic plasticity (de la Fuente Revenga et al., 2021; Desouza et al., 2021; Ly et al., 2018). See **Fig. 3** taken from Ly et al. 2018.

It is of interest to all parties involved that we achieve a scientific understanding of the mechanisms of action of these compounds, which will be widely used in psychiatric settings within a matter of years (Nutt & Carhart-Harris, 2021).

Recommendations

1) Maintain the current non-scheduled status of DOI and DOC to expedite research into 5-HT_2 receptors and their influence on disease states and chronic pain.

2) Establish a new framework to remove Schedule 1 DEA licensing requirements for any laboratories with a Schedule II licence, allowing them to study Schedule 1 substances. Restrictions on researching Schedule 1 substances places undue and strenuous burden on researchers, an opinion shared by Dr. Nora Volkow, the Director of the National Institutes of Drug Abuse, and others in the research community (*Statement of Nora Volkow, M.D. Hearing on Cannabis Policies for the Next Decade*, 2020). In the context of DOI and DOC, the DEA's own position is that these drugs do not appear "on the streets" via illegal dispersal from scientific research laboratories (Drug Enforcement Administration, 2023a), so this modest allowance is unlikely to increase the amount of illegally trafficked DOI and DOC.

This document is drafted and signed by the following:

Tanner L. Anderson, B.S. (Biology, University of Kentucky) is a PhD candidate and NRSA F31 Fellow (NIDA) from the Ortinski Lab in the Department of Neuroscience at the University of Kentucky. He uses DOI as a 5-HT_2 receptor-specific drug to study the potential therapeutic effects of psychedelics on cognitive flexibility in models of cocaine use disorder. Additionally, he uses DOI to characterise 5-HT receptors and psychedelic-induced plasticity in the claustrum, a brain region that has gained recent increased research excitement due to its implications in a variety of behaviours and psychiatric diseases such as substance use disorder. As an NIH NRSA F31 Fellow, Tanner has received funding from the National Institute on Drug Abuse specifically to study the mechanisms underlying the therapeutic potential of DOI. A reclassification of DOI into Schedule 1 would completely halt the culmination of a 5 year research project that is providing valuable insights into the role of serotonin receptors, the function of a poorly understood brain region, and possible neurophysiological underpinnings responsible for the therapeutic effects of psychedelic drugs.

Anousheh Bakhti-Suroosh, B.S., PhD Candidate (Neuroscience, University of California San Diego) in the Tye Lab at the Salk Institute for Biological Studies and co-founder of Students for Sensible Drug Policy at UCSD. Anousheh's research utilizes systems and computational approaches to understand how psychedelics such as psilocybin and DOI alter neural representations of emotional valence and social interaction.

Devin P. Effinger, Ph.D (Pharmacology, University of North Carolina Chapel Hill) is a postdoctoral fellow working with Scott Thompson, Ph.D in the Laboratory of Translational Psychiatry within the Department of Psychiatry at the University of Colorado Anschutz Medical Campus. His doctoral research investigated the effects of psilocin administration on stress related brain region reactivity and behavioural responding. Currently, Dr. Effinger's research is investigating neurophysiological mechanisms underlying depressive-like behaviours such as anhedonia and how psychedelics such as LSD affect these processes. Additionally, Dr. Effinger is a member of the clinical team in the Department of Psychiatry that will begin recruiting for an fMRI clinical trial testing the efficacy of psilocybin on implicit reward related tasks and symptom outcomes within individuals diagnosed with treatment resistant depression.

Tyler G. Ekins, PhD (Neuroscience, Brown University), is a postdoctoral Research Fellow at University of Michigan, and a Michigan Psychedelic Center Collaborator. Dr. Ekins studies the acute and sustained effects of 5-HT_2 receptor agonists/psychedelic drugs, including the critically useful preclinical gold research standard and

selective 5-HT_2 receptor agonist DOI, on neuronal electrophysiology. DOI being classified as a Schedule 1 drug would do substantial damage to this research.

Christopher W. Fields, B.S. (Neuroscience, University of Michigan), is a PhD student in the Institute of Neuroscience at the University of Oregon. Christopher uses DOI as a tool to study the role of 5-HT_2 receptors in modulating sensory processing. As a former Research Associate at the University of Michigan, he also used DOI to investigate the role of these receptors in mediating conscious state transitions and altering functional connectivity across the brain. DOI is an essential tool for these lines of research because its effects on neural population and circuit dynamics have been more thoroughly characterised than any other unscheduled psychedelic compound, and loss of this compound due to schedule I status would disrupt the continuity of this research.

Joseph J. Hennessey, B.S., is a medical student in the Medical Scientist Training Program at the Medical College of Wisconsin pursuing a dual MD/PhD degree. With Dr. John McCorvy, Joseph screened thousands of known psychedelics—including DOI—and novel compounds for activity at G-protein coupled serotonin receptors. Joseph plans to use DOI and other psychedelics in his dissertation work examining the cellular and circuit neurobiology of psychedelic drug action. As one portion of the project will involve investigation of how psychedelic polypharmacology impacts therapeutic outcomes, DOI is an essential component of the planned studies, as it is more selective for 5-HT_2 receptors than almost any other known compound and has an extensively characterised metabolic and off-target profile.

Alaina M. Jaster, PhD (Pharmacology and Toxicology, Virginia Commonwealth University), is currently transitioning to a postdoctoral position in the Department of Psychiatry at Wayne State University. Her PhD dissertation focused on the molecular and neural circuits involved in DOI and psilocybin's effects in preclinical models of opioid-reward. She is a member of the Scientific Policy Council for Students for Sensible Drug Policy, member of Trainee Editorial Board for *Psychedelic Medicine* (a scientific journal focused specifically on basic and clinical research of psychedelics) and the founder and host of *Your Brain on Science,* a podcast and website focused on bringing psychedelic science to the public.

Raul A. Ramos, PhD (Neuroscience, Brandeis University), is a Hanna Gray Fellow with the Howard Hughes Medical Institute (HHMI) and a Miller Postdoctoral Fellow with the Miller Institute for Basic Research in Science at the University of California, Berkeley. Dr. Ramos's research focuses on understanding the effects of psychedelics on the peripheral nervous system and their ability to alter our sense of touch, itch, and pain. The results of this work have the potential to significantly inform the development of psychedelic-assisted therapies. Currently, Dr. Ramos is the recipient of an 8-year-long grant awarded by HHMI and dedicated to the study of DOI. However, he is not approved to work with Schedule I substances. If this proposed rule is enacted, Dr. Ramos's ability to follow through on the research that he is funded to work on will become totally obstructed.

Elijah Z. Ullman, B.S., PhD Candidate (Molecular and Systems Pharmacology, Emory University), is Chair of the Science Policy Council of Students for Sensible Drug Policy, a 2023 American Society for Pharmacology and Experimental Therapeutics (ASPET) Washington Fellow, and a member of the ASPET Drug Research Policy Committee, and Washington Fellows Program Committee. His dissertation research focuses on the pharmacology underlying allosteric modulation of the NMDA Receptor and dynamics of the ion channel pore. Although Elijah does not utilise DOI or DOC in his work, he is concerned with any effort that aims to stifle the scientific community's efforts to develop novel therapeutics for depression, PTSD, and pain management.

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January 12, 2024

Drug Enforcement Administration
Attn: OALJ
8701 Morrissette Drive
Springfield, Virginia 22152

Re: Request for Hearing in the matter of Docket No. DEA-1156

Dear Madam:

The undersigned counsel, on behalf of Dr. Raul A. Ramos, Amelia A. Furbish, PharmD, and Megan Francis, hereby submit this request for a hearing in the matter of: Placement of 2,5-dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-chloroamphetamine (DOC) in Schedule I (DEA1156).

Interest in the Proceedings.

Dr. Raul A. Ramos is the 2023 Howard Hughes Medical Institute Hanna Gray Fellow and the Miller Postdoctoral Fellow at the Miller Institute for Basic Research in Science at the University of California, Berkeley. Dr. Ramos has been awarded a grant of $1.5 million to research the neural mechanisms relating to Sensory Processing Disorder (SPD). SPD impairs social attachment, adaptive skills, and academic learning, ultimately compromising mental health and independent living. Dr. Ramos' research will be severely hindered and may be unfeasible if DOI is added to Schedule 1 status.

Ms. Furbish is a Doctor of Pharmacy involved in research evaluating the potential risk of cardiac valvulopathy and pulmonary hypertension associated with serotonergic compounds. This proposed rulemaking would have a profound detrimental impact on her ability to investigate the role of serotonergic signaling on human pathology and would significantly hinder scientific research efforts relating to toxicology, pharmacology, and drug discovery.

Ms. Francis is a Neuroscience PhD student specializing in addiction neuroscience and psychedelic drugs. She is part of a research group that recently completed a series of experiments resulting in extensive unpublished preclinical data to suggest that DOI has therapeutic value in the treatment of opioid use disorder and demonstrated the remarkable ability to induce lasting reductions in relapse and heroin-seeking behavior in a mouse model of opioid addiction. Her research would be rendered virtually impossible if these compounds were placed into Schedule I and would halt important medical research that has a significant impact in the areas of neuroscience and pharmacology.

Objections to the Scheduling of DOI and DOC.

1. DOI is currently the standard reference for determining binding affinity at 5-HT2B receptors and determining serotonergic receptor distribution in vivo. In addition, DOI is the only compound that has been extensively validated across multiple experimental

models, emphasizing the importance of its use within the scientific community and in current toxicologic studies. This proposed rulemaking would have a profound detrimental impact on researchers' ability to investigate the role of serotonergic signaling on human pathology and significantly hinder scientific research efforts across toxicology, pharmacology, and drug discovery.

2. If DOI is designated a Schedule 1 drug, the licensing and specialized facility requirements to conduct research will raise the expense of this research and create significant barriers in collaboration with other laboratories that do not possess the necessary licenses. Research frequently involves working with contract research organizations and other academic laboratories for specialized experiments. Many of these laboratories are inexperienced in managing scheduled substances and are not motivated to engage in the complex procedures required to acquire and maintain a license or lack the financial resources to do so.

3. No credible high abuse potential, a threat to public safety, or dependence regarding DOI has been demonstrated. No documentation regarding DOI of even a modest frequency of use has been presented. DOI has never been implicated in a single human death or hospitalization. DOI and DOC do not exhibit addictive properties as they do not engage dorsal striatal circuitry, which is the main neural mechanism underlying the reinforcing properties of addictive drugs of abuse, such as opioids, cocaine, and alcohol. DOI and DOC drugs appear to pose little physiological risk and do not appear to have reinforcing properties. There is a significant body of clinical and preclinical literature suggesting that DOI and other serotonin 2A agonists have therapeutic value for the treatment of a wide range of disorders including, but not limited to, depression, anxiety, Post-Traumatic Stress Disorder, and substance use disorders. HHS stated that physiological dependence liability of DOI and DOC in animals and humans is not reported in scientific and medical literature and that it is not possible to determine whether DOI and DOC produce physiological dependence following acute or chronic administration.

4. Diversion for use outside of legitimate scientific research has not been demonstrated. HHS stated: "DOI and DOC are available for purchase from legitimate chemical synthesis companies because they are used in scientific research. There is no evidence of diversion from these companies."

5. The application of the §811(b) Eight Factor analysis has been applied in a way that is arbitrary, capricious, contrary to law, or lacks substantial evidence. The §811(b) analyses

repeatedly makes improper conclusions based on unsubstantiated statements, insufficient evidence, and is sometimes even contradicted by data from HHS.

6. The finding that a substance lacks accepted medical use is not dispositive for purposes of classification.

7. There is no known report of DOI or DOC dependence anywhere in forensic or medical literature. The DEA relies on anecdotal reports of DOI and DOC abuse published anonymously online and thus utterly unverifiable. Anonymous online comments and reports that are unverifiable do not firmly demonstrate abuse or even use of DOI or DOC.

8. The potential medical value of DOI, DOC, and other psychedelics is significant and warrants further investigation, which would be rendered impossible for many laboratories if these compounds were placed into Schedule I, and curtailing important medical research that has a significant impact in the areas of neuroscience and pharmacology.

For these reasons, the petitioners believe that the scheduling of DOI and DOC would not protect the public from harm. As these compounds are essential to scientific research that is striving to address some of the most critical national health issues, including mental health and opioid addiction, it would likely place the public's health in greater jeopardy by impeding access to these drugs by researchers.

For these reasons, the petitioners request that the DEA withdraw or delay the proposed rule.

As counsel of record for petitioners, I ask that all notices to be sent pursuant to the proceeding should be addressed to:

Law Office of Robert T. Rush
600 17th Street
Suite 2800 South
Denver, CO 80202

Respectfully yours,

Robert T. Rush