IND 110513

APPEAL DENIED

Multidisciplinary Association for Psychedelic Studies (MAPS)
Attention: Rick Doblin, PhD
Founder and President
3141 Stevens Creek Blvd #40563
San Jose, CA 95117

Dear Dr. Doblin:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for marijuana, *Cannabis sativa* or *indica* (containing delta-9-tetrahydrocannabinol and cannabidiol).

I also refer to your August 23, 2024, request for formal dispute resolution received on August 23, 2024. The appeal concerned the Continue Partial Clinical Hold letter issued for your application by the Division of Psychiatry (DP) on December 28, 2023, which cited four hold issues:

1. The proposed dose of your cannabis product.
2. Smoking as a delivery method.
3. Vaping as a delivery method.
4. Enrollment of subjects who have not previously inhaled cannabis.

I have carefully reviewed the materials you submitted in support of your appeal, as well as meeting minutes from the Type A meeting held on June 15, 2023, Protocol MJP2 Version 1, Amendment 2 dated November 17, 2023, and the Continue Partial Clinical Hold letter issued on December 28, 2023. I have also consulted with Staff in the Division of Psychiatry and Division of Pulmonology, Allergy and Critical Care (DPACC).

I have completed my review of your request for formal dispute resolution and deny your appeal. I describe below the basis for my decision and provide recommendations for a possible path forward.

There have been recent internal discussions regarding potential pathways to allow research of cannabis products using smoking or vaping as a delivery method under INDs; however, there had not been adequate time to convey the outcome of these discussions to you prior to receiving your Formal Dispute Resolution Request.

1. Regarding the proposed dose of your cannabis product, DP has concluded that the justification provided for the proposed dose of cannabis in Version 1, Amendment 2 Protocol MJP2 dated November 17, 2023 (i.e., 1.5 g/day cannabis

with 20-22% THC (300-330 mg), is acceptable and this is no longer a hold issue for this protocol. However, high potency cannabis, commonly defined as having a content of THC above 15%, is associated with higher risk of psychosis and addiction.[1] The risk should be described in the informed consent document.

2. Although smoking and vaping are not safe, DP has determined that smoking and vaping do not represent an unreasonable risk for people with a serious condition, such as PTSD, who already engage in this behavior—provided the risks of smoking and vaping are adequately discussed in the informed consent process and reflected in the informed consent document.

   I also note your contention on page 31 of the appeal document that EVALI is not applicable to the evaluation of risk because study MJP2 uses dried cannabis product and does not contain other additives or fillers, such as Vitamin E acetate. EVALI is linked to vaping devices. While additives have been linked to EVALI, the etiology of EVALI has not been fully elucidated. Therefore, the risks of EVALI with vaping need to be described in the informed consent document.

3. The protocol must contain adequate patient selection criteria to ensure that subjects are not exposed to unreasonable and significant risk.. I agree with DP that the inclusion of subjects who are "considering inhaling cannabis at the time of study enrollment" is not acceptable. There is a lack of clinical equipoise in randomizing patients who are in the contemplative phase of initiating smoking or vaping. Subjects who are not current smokers or vapers but are "considering inhaling cannabis at the time of study enrollment" must be excluded from your study.

You may submit a complete response to clinical hold to your IND that references this formal dispute resolution decision letter and contains an updated informed consent document and protocol that adequately addresses the points above. Additionally, please refer to the Appendix for specific recommendations regarding patient selection, safety monitoring, and documentation of informed consent for your IND.

Questions regarding next steps as described in this letter should be directed to Iram Baig, Regulatory Health Project Manager, Division of Regulatory Operations for Neuroscience- Psychiatry at [redacted].

This constitutes the final decision at the Office of Neuroscience level. If you wish to appeal this decision to the next level, your appeal should be directed to Peter Stein, MD, Director, Office of New Drugs, Center for Drug Evaluation and Research. The appeal should be sent to the IND administrative file as an amendment, and a copy should be sent to the Center's Formal Dispute Resolution Program Manager, Melissa Sage.

---

[1] Petrilli K, Ofori S, Hines L, Taylor G, Adams S, Freeman TP. Association of cannabis potency with mental ill health and addiction: a systematic review. Lancet Psychiatry. 2022 Sep;9(9):736-750. doi: 10.1016/S2215-0366(22)00161-4. Epub 2022 Jul 25. PMID: 35901795.

Any questions concerning your appeal should be addressed to Melissa Sage at [redacted] or via e-mail at [redacted].

Sincerely,

{See appended electronic signature page}

Teresa Buracchio, MD
Director
Office of Neuroscience
Center for Drug Evaluation and Research

Appendix. Recommendations for Patient Selection, Safety Monitoring, and Informed Consent

Patient Selection

- The American Thoracic Society and American Lung Association strongly recommend against smoking or vaping for anyone, but particularly in people with an existing lung disease, such as COPD or asthma. Patients with underlying lung disease should be excluded from study, if feasible for the indication.

Safety Monitoring

- Pulmonary symptoms, such as cough and dyspnea, should be pre-specified as adverse events of special interest (AESIs), and the investigators should outline a plan to actively elicit these AESIs.
- Pulmonary-related stopping criteria and participant discontinuation should be pre-specified.
- Safety follow-up should include monitoring for 90 days after the last exposure since the risk for EVALI is greatest within 90 days of use.

Informed Consent

- The informed consent should clearly document the risks of lung injury for smoking and all vaping products regardless of the mode of delivery. The risks should mention EVALI (e-cigarette or vaping use-associated lung injury), a serious form of lung injury, that can lead to irreversible inflammatory lung damage and result in hospitalization or death. The informed consent should highlight the higher of risk of EVALI in current/former smokers.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TERESA J BURACCHIO
09/19/2024 01:55:48 PM