Multidisciplinary Association for Psychedelic Studies
3141 Stevens Creek Blvd. #40653
San Jose, CA 95117 USA
maps.org

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Tiffany R. Farchione, M.D.
Director, Division of Psychiatry Products
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
[redacted]
Beltsville, MD 20705-1266

CONTINUED CLINICAL HOLD COMPLETE RESPONSE

RE: IND #110513, Serial No. 0036, Study MJP2 Continued Clinical Hold Response Letter

Dear Division of Psychiatry Products,

Please see the below response to the hold issues in the Agency's Continued Partial Clinical Hold Letter dated 28 December 2023 (PCH-5, Ref ID 5301553) for the MAPS-sponsored Study MJP2, entitled "*Phase 2 Multicenter Randomized Placebo-controlled, Double-blind, Parallel Study to Assess the Safety and Efficacy of Inhaled Cannabis in Veterans for Treatment of Posttraumatic Stress Disorder (PTSD)*."

This response incorporates the additional guidance and updates on hold issues received from the Agency's Dispute Appeal Denied Letter dated 19 September 2024 (Ref ID 5449384) which is also referenced here.

Hold Issue: 21 CFR 312.42(b)(2)(i): Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury

PCH-5 Hold Issue 1: *You have not provided adequate data to support the safety of the proposed dose of your cannabis product for use as directed in the amended protocol. Specifically, the safety of the maximum daily dose of THC is not supported by the scientific literature you submitted. To resolve this deficiency you must use a dose less than or equal to the highest dose you used in your pilot study MPJ1, or propose to conduct a phase 1 dose escalating study to characterize the clinical safety of higher THC doses.*

The Appeal Denied Letter from the Office of Neuroscience, included the following update regarding PCH-5 Hold Issue 1:

> ***ON Response to Hold Issue 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. The risk should be described in the informed consent document.*

Sponsor Response to Hold Issue 1: The Sponsor acknowledges the updated conclusion of the Division that the proposed dosing strategy in MJP2 Protocol A2V1 dated 17 November 2023 of 1.5 g/day cannabis with 20-22% THC (300-330 mg), is acceptable and is no longer a hold issue for this protocol.

In keeping with the guidance on informed consent, the Sponsor has accordingly updated the ICF and

study protocol to note the increased risks observed with high potency THC specifically noting "*Compared to lower potency cannabis, higher potency cannabis (>15% THC), like the cannabis typically sold in dispensaries and used in this study, is associated with a higher risk of psychosis and addiction."*

Please see the enclosed updates to the MJP2 ICF V2.2, dated 07Oct2024 for the full text of the updated ICF and the MJP2 Protocol A2V2, dated 07OCT2024.

PCH-5 Hold Issue 2: *Smoking is not a safe drug delivery method. Smoking is harmful to the lungs; the available evidence demonstrates that pre-rolled cigarettes as a cannabis delivery method is harmful to the lungs. While we note that you are proposing this study as a research protocol, the risks associated with smoking, as outlined in previous comments dated July 31, 2023, remain unchanged. To resolve this deficiency, you must change the drug delivery method in your protocol.*

The Appeal Denied Letter from the Office of Neuroscience, included the following update regarding PCH-5 Hold Issue 2:

> ***ON Response to Hold Issue 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.*

Sponsor Response to Hold Issue 2: The Sponsor acknowledges the updated conclusion of the Division 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.

The Sponsor has updated the protocol inclusion criteria to reflect that all participants will be required to have prior experience inhaling (smoking or vaping) cannabis. Please see the enclosed update to the MJP2 Protocol A2V2, dated 07OCT2024.

PCH-5 Hold Issue 3: *Vaping is not a safe drug delivery method. There are pulmonary safety concerns associated with vaping regardless of the device used. Vaping is harmful to the lungs. Although more research is in this area is needed, some evidence suggests that these risks may be higher for former tobacco/cannabis smokers. To resolve this deficiency, you must change the drug delivery method in your protocol.*

The Appeal Denied Letter from the Office of Neuroscience, included the following update regarding PCH-5 Hold Issues 3:

> ***ON Response to Hold Issue 3:*** *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.*

Sponsor Response to Hold Issue 3: The Sponsor acknowledges the updated conclusion of the Division 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.

The Sponsor has updated the protocol inclusion criteria to reflect that all participants will be required to have prior experience inhaling (smoking or vaping) cannabis and has ensured that the risks of smoking and vaping are reflected in the ICF in keeping with the guidance from the Agency. Please see the enclosed update to the MJP2 Protocol A2V2, dated 07OCT2024.

The Sponsor's understanding is that evidence indicates that the emergence of e-cigarette and vaping-associated lung illness (EVALI) was specifically associated with regionally distributed vaping products due to the fillers added to the e-liquids, such as Vitamin E acetate (Blount et al., 2020; MacCallum et al., 2024). The Sponsor believes that the risks of cannabis inhalation with dried cannabis flower vaporizers differ from vaporizing e-liquids or concentrates which may include these additives (Blount et al., 2020; MacCallum et al., 2024. Specifically, EVALI cases were documented in high-prevalence regional clusters rather than in patterns reflecting overall vaping or cannabis use as would be expected if driven by broadly mass-marked devices (Friedman, 2021). We are unaware of any evidence directly supporting a connection between EVALI and the vaporization of dried cannabis flower (without additives).

However, the Sponsor acknowledges the Agency's assessment is that the etiology of EVALI has not been fully elucidated, and therefore the risks of EVALI should be included for Study MJP2. In keeping with the Agency's updated guidance, the Sponsor has added additional language to the ICF regarding the potential risk of EVALI as, "*A serious form of lung injury called EVALI (E-cigarette, or Vaping, product use Associated Lung Injury) that can lead to irreversible inflammatory lung damage and result in hospitalization or death has been associated with the use of "vaping devices." While researchers have linked an additive (vitamin E acetate) found in some vaping products to EVALI, this condition is not fully understood. A connection between EVALI and the vaporization of cannabis flower (without additives) has not been established and it is possible that one may exist.*"

Please see the enclosed MJP2 ICF V2.2, dated 07Oct2024.

PCH-5 Hold Issue 4: *Naïve participants, even though they are considering starting, are non-users for the purpose of determining their level of risk. The safety of exposing cannabis naïve participants to your cannabis product is unknown. To resolve this deficiency, you must exclude subjects who are naïve cannabis smokers.*

The Appeal Denied Letter from the Office of Neuroscience, included the following update regarding PCH-5 Hold Issue 4:

> ***ON Response to Hold Issue 4:*** *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.*

Sponsor Response to Hold Issue 4: The Sponsor acknowledges that the ON agrees with the Division that cannabis naive PTSD patients would be "*exposed to unreasonable and significant risk*" if randomized in this study to smoking / vaping cannabis in an amount of their choosing for a 5-week

period.

While the Sponsor disagrees with the characterization of this risk in cannabis naive participants as "unreasonable and significant," in keeping with email correspondence the Sponsor has updated the protocol inclusion criteria to reflect that all participants will be required to have "*prior experience inhaling (smoking or vaping) cannabis.*" The Sponsor has removed all references of inclusion of cannabis naive participants who are "*considering inhaling cannabis at the time of study enrollment."* Please see the enclosed update to the MJP2 Protocol A2V2, dated 07OCT2024.

We appreciate the engagement of the ON and reconsideration of some of these issues by the Division. We hope that in light of the previous discussions at our Type A Meeting in June 2023, the contents of our FDRR packet, and the updates made herein in light of the Appeal Denied Letter from the Office of Neuroscience, that the Division will find these outstanding hold issues to be resolved and permit Study MJP2 to proceed. If any questions arise during the Division's review of the submission that require further clarification in support of a resolution, please don't hesitate to contact Allison Coker by email at [redacted].

Sincerely,

Rick Doblin

Rick Doblin (Oct 8, 2024 13:20 EDT)

Rick Doblin, Ph.D.
Founder and President
MAPS

References

Blount, B. C., Karwowski, M. P., Shields, P. G., Morel-Espinosa, M., Valentin-Blasini, L., Gardner, M.,…Group, L. I. R. L. W. (2020). Vitamin E Acetate in Bronchoalveolar-Lavage Fluid Associated with EVALI. *N Engl J Med*, *382*(8), 697-705. https://doi.org/10.1056/NEJMoa1916433

Friedman, A. S. (2021). Association of vaping-related lung injuries with rates of e-cigarette and cannabis use across US states. *Addiction*, *116*(3), 651-657. https://doi.org/10.1111/add.15235

MacCallum, C. A., Lo, L. A., Pistawka, C. A., Christiansen, A., & Boivin, M. (2024). Cannabis vaporisation: Understanding products, devices and risks. *Drug Alcohol Rev*, *43*(3), 732-745. https://doi.org/10.1111/dar.13800