IND 110513

CONTINUE PARTIAL CLINICAL HOLD

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

Dear Rick 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* (containing delta-9-tetrahydrocannabinol and cannabidiol).

We also refer to your amendments dated November 29 and December 10, 2021, and August 16 and November 16, 2022, and November 30, 2023, that provide a response to our May 10, June 3, and December 27, 2021, and December 16, 2022, letters which cited the reasons for placing Protocol MJP2, "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)," on clinical hold and the information needed to resolve the clinical hold issues.

We have completed the review of your submissions and have concluded that removal of the clinical hold from the following proposed study is not warranted. Specifically, the following issues have not been resolved:

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

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.

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.

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.

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.

Therefore, the clinical hold on Protocol MJP2 remains in effect until you have submitted the required information and we notify you that you may initiate this clinical study, you may not legally conduct this study under this IND.

Please identify your response to the clinical hold issues as a "**CLINICAL HOLD COMPLETE RESPONSE**."

Following receipt of your complete response to these issues, we will notify you of our decision within 30 days.

We have the following additional comments and recommendations regarding your study protocol:

CLINICAL

1. Even though your study is not intended to support a commercial development, it is still an interventional study for effectiveness and safety evaluation; therefore, the Agency reiterates that self-titration is not an optimal dose regimen for interpretability of study data. However, the Agency could accept a flexible self-tapering of the proposed cannabis regimen providing that agreement is reached on the maximum daily dose of THC allowed for administration (please refer to clinical hold comment #1).

2. We reiterate that you should include subject-level and study-level stopping criteria in your protocol referencing known safety risks associated with your cannabis product with high THC.

3. You should assess and monitor suicidal ideation and behavior (SIB) at baseline (screening) and at all planned visits at which other clinical assessments are to be carried out. You should use of an assessment instrument that directly classifies relevant thoughts and behaviors into Columbia Classification Algorithm for Suicide Assessment (C-CASA) categories. Please refer to the draft FDA guidance for industry, *Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials*, for more information.

4. We recommend participants should not consume more than 1 g of the cannabis product in a 6-hour period.

5. We recommend you monitor EKG for all participants.

6. We recommend you perform a urine pregnancy test for females of childbearing potential at V3.

7. Although you note a physician is available by phone or onsite during Introductory Sessions, please clarify if a physician will be available in the event of an emergency.

8. You should add vital signs to your V6 schedule of activities and pulse oximetry to V4 and V5.

9. Please justify why participants must have a negative urine toxicology screen for cannabis in order to enter the study given that you are recruiting cannabis users for the study.

10. Please correct the dose you specify in footnote G of your schedule of activities table.

11. Please justify why a urine toxicology test cannot be performed at V4 by an unblinded researcher whose role is to monitor for potential diversion and can communicate the results of the urine toxicology test to the blinded research team excluding the THC results to retain the blind. Participants diverting study drug should not be allowed to receive a resupply of study drug and should be withdrawn from the study.

12. We recommend you do not allow participants to receive a supply for any drug they did not use over the course of the study at the end of the study.

Informed Consent Document (ICD) comments:

1. You specify in your ICD, “If you become pregnant, you will be withdrawn from receiving additional study drug.” You should add that all unused study drug must be returned.

2. Please resolve inconsistencies between your ICD and protocol in regard to the number of days after the End of Treatment visit participants who are able to become pregnant must continue birth control.

3. Please resolve inconsistencies between your ICD and protocol in regard to length of resupply.

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH)

Please refer to clinical hold comment #2 related to the safety of vaping as a drug delivery method. In relation to the use of the PAX2 vaporization device, although you have provided a Letter of Authorization to reference IND [redacted], the submission does not contain a Device Master File that demonstrates the safety of the device. This information is required because an unsafe vaporization device can cause harmful chemicals to leach from the device into the patient airway and cause lung irritation or long-term tissue damage. Therefore, the following information to demonstrate the safety of the PAX2 vaporizer is required for sponsors who consider using the device in clinical development prior to submitting a phase 3 proposal or pre-marketing application:

- Device Description
- Intended Use
- Clinical Labeling
- Biocompatibility
- Performance Testing
- Electromagnetic Compatibility and Electrical and Thermal Safety
- Human Factors/Usability Testing
- Reprocessing/Sterility information
- Software Description (if applicable)

CDRH, Office of Product Evaluation and Quality

1. Provide a device description of the proposed vaporizer. Examples of key characteristics that should be provided as part of your device description include, but are not limited to, the following features:

    a. Provide a detailed device description and identify all components and accessories of the device proposed to deliver the drug substance. Include diagrams, dimensions, tolerances, and/or schematics for each device, accessory, or component.

    b. Identify all patient interface accessories and provide engineering drawings which show any breathing holes and/or valves. Indicate whether each accessory is intended for single use, single-patient reuse, or multi-patient reuse.

    c. Illustrate and explain the breathing gas path, including all valves and orifices, during inhalation and exhalation.

    d. Identify the materials of composition for your device. For many devices, a complete identification of the detailed chemical formulation used in the materials of construction, especially for those materials that come into contact with the patient, should be provided. Note that the FDA does not clear/approve materials.

e. Any additives, including color additives, coatings, or other surface modifications should also be identified. For some devices, the processing of the material (e.g., forged vs. cast) or the state of the material (e.g., amorphous vs. crystalline) may also significantly contribute to or affect the overall safety or function of the device, and so should be included as part of the device description, as applicable.

f. Describe your device's energy sources. We note that your device generates considerable heat for vaporization of the drug. It is important that you provide sufficient detail regarding your device's energy sources. This not only includes energy delivery to the device, including the use of batteries, but also energy delivery that is part of the functional aspect of the device (e.g., laser, radiofrequency, ultrasound, etc.) and that affects the patient and/or the health care professional using the device.

g. Describe all other key technological features. These include, but are not limited to, software/hardware features, density, porosity, degradation characteristics, nature of reagents (recombinant, plasma derived, etc.), principle of the assay method, etc., that are not explicitly included as part of the materials, design or energy source characteristics. These technological features should be included as part of the device description, as appropriate for your specific device's technology.

h. Provide a detailed description of the heating and cooling processes of the device.

2. Provide information regarding the biocompatibility of your device. It is important that you determine the potential for unacceptable adverse biological responses for medical devices that come into direct and/or indirect contact with the human body. Without such information, the Agency cannot review your device's safety and is uncertain whether concerns of undue risk to the patient are raised. As such, Provide the following information:

   a. For each patient contacting device component, identify the contact classification (e.g., surface-contacting, less than 24-hour duration). Note that FDA considers the device components which contact the gas pathway of the patient or the aerosolized drug as external communicating components with tissue contact.

   b. Provide all applicable biocompatibility information for your device, per the Agency's guidance "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within the risk management process," available at https://www.fda.gov/media/85865/download.

   c. Provided sufficient information in order to assess the air quality of your device. The potential exists for your device to adulterate the air being delivered to the patient either through manufacturing residues, chemical processes, or

mechanical degradation. Therefore, we recommend you evaluate the air quality of your device per the ISO 18562 series standards in order to determine whether it may produce potentially harmful gases, volatile organic compounds (VOCs), or particulates.

3. Provide validation of your device's electrical safety and robustness. As such, validate your device's electrical safety and provide testing per the applicable clauses of ANSI/AAMI ES60601-1: Medical Electrical Equipment General Requirements for Safety.

4. Provide the validation of your device's electromagnetic compatibility. Without such information, the Agency is unable to review your device's safety per your intended use. As such, provide the following information:

   a. The environments defined by the manufacturer for which the medical device is intended to be used.

   b. A summary of the testing that was performed to support EMC.

   c. The specifications of the standard that were met (including immunity test levels).

   d. A summary of the device-specific pass/fail criteria used, including how the pass/fail criteria were derived. Each medical device should have specific criteria based on the device functions, indications, intended use, and essential performance. Particular device standards (e.g., IEC 60601-2-X, ISO 14708-3) may contain device-specific test methods and pass/fail criteria that can also be referenced.

   e. The specific functions of the device that were tested (e.g., for IEC 60601-1-2, this should include performance that was determined by the manufacturer to be essential performance) and how these functions were monitored during testing. For example, use quantitative measurements and visual observation to monitor the specific functions of the medical devices. The monitoring system should not perturb the test.

   f. Specific information about the performance of the device during each test demonstrating that the device met the emissions and immunity pass/fail criteria. This includes a summary of any device effects, disruptions, or degradations observed during testing and how these were mitigated (see point j below).

   g. An identification of and a justification for any of the standard's allowances that were used, if applicable.

h. A description of and justification for any deviations from the specifications of the referenced standard. The justification should explain how the deviations would not compromise the safety and effectiveness (performance) of the device.

i. The device labeling and evidence of compliance with the reference standard's labeling (identification, marking and documents) specifications.

j. A detailed description of all changes or modifications that were made to the tested version of the device in order to pass any of the EMC tests. If modifications were made, a statement should be included in the premarket submission indicating that the changes or modifications will be incorporated into the legally marketed version of the device prior to marketing and documented in the design history file in accordance with design controls. In addition, you should assess whether these modifications might impact other aspects of the device performance (e.g., biocompatibility) and provide information in the device description section of the submission to demonstrate that the modifications would have no impact on the other aspects or that the modified device was used for the other performance tests.

5. Provide a description of whether your device contains software. It is important that you provide sufficient information to demonstrate your device's safety and mitigation of any software risks for your proposed intended use. This information should include validation of any software included in your device. As such, specify the extent to which your device contains software. Provide all the relevant information requested in the Agency's guidance document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices", available at https://www.fda.gov/media/73065/download.

6. Provide performance data for validation and verification of your device specifications. You have not provided any testing to characterize the aerosol output of your device to proceed with your proposed study. It is recommended that you conduct this testing with a cascade impactor consisting of at least six stages. If the device is intended for use with a range of flow rates, you should conduct complete particle size distribution testing at the maximum and minimum flow rates. Test reports should include the following:

   a. The original dose volume in micrograms of drug.

   b. The amount of drug in micrograms recovered on each impactor plate, throat, and outlet filter.

   c. The drug mass recovered in the cascade impactor in the respirable size range (i.e., 0.4-4.7 or 0.5-5 microns, depending on the type of impactor used) expressed as a percent of the total drug mass in the nebulizer cup.

d. The mass median aerodynamic diameter (MMAD- the diameter above and below which lies 50% of the mass of the particles) of the particles recovered in the impactor.

e. The geometric standard deviation of the MMAD.

f. Provide data characterizing the potential effect of inter-sample variability on the dose specifications in your labeling. Specify the number of device samples that were used in your performance tests and provide a statistical analysis explaining why this number of samples is sufficient to demonstrate with an appropriate level of confidence that (1) variability in individual device samples do not noticeably affect the dosing specifications of the proposed device and that (2) develop confidence for particle specifications overall, irrespective of inter-sample variability.

g. In analyzing the results of the tests cited above, provide a justification of why the levels of variability shown are appropriate for the use of the devices in delivering the proposed drug formulation.

7. Provide a simulated use testing for your device. We are uncertain how long your device and its accessories are intended to be used based on the limited information provided. Without such information, the Agency cannot adequately review your device's safety and the appropriateness of your proposed use in this study. Provide clarification if you have performed simulated use testing to show that your vaporizer and all accessories perform as intended when used continuously for the recommended duration of use, and provide the testing.

8. Provide a stress testing for your device. We are uncertain whether your device and its accessories can function as intended over its duration of use when exposed to reasonably expected mechanical stresses. Without such information, the Agency cannot adequately review your device's safety and the appropriateness of your proposed use in this study. As such, provide the full test reports for shock, random vibration, and bump tests.

9. Provide a discussion on your device's reusability and any applicable reprocessing measures required during its use. We are uncertain whether your device can be successfully reprocessed and can function as intended when exposed to necessary reprocessing measures required for its continued use. Without such information, the Agency cannot adequately review your device's safety and the appropriateness of your proposed use in this study. As such, provide all reprocessing information requested in the Agency's guidance document "Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling," available at https://www.fda.gov/media/80265/download.

10. Provide a usability testing or human factors discussions. Due to the nature of Human Factors, each application requires unique consideration. When applying an existing device to a new use scenario, there is potential for the introduction of new use errors and new risks, based on changes to intended users, uses, and use environments. The Agency expects human factors data obtained from appropriate human factors and usability (HF-U) validation testing (also referred to as summative testing), to detail how the final design of the user interface (including training and user documentation) supports user needs for safe and effective use considering intended users, uses, and environments of use.

    In your submission, provide documentation containing, or new information as necessary, for the following:

    a. An overview of intended device users or user populations and considerations for any unique or compelling characteristics regarding knowledge, expectations, capabilities, training, or experience that could limit their ability to interact with the device user interface (UI).

    b. A depiction and description of the device user interface UI and overview of user interaction with the UI during use.

    c. Consideration of the device use environment and its potential to impact the ability of users to use the device successfully (e.g., background noise could obscure audible information or alarms).

    d. A summary of known use problems for predecessor or similar devices.

    e. An analysis of user tasks including assigning criticality to tasks for which inadvertent use error (including failure to perform the task) could or would cause clinical harm. Identified “critical tasks” should be the focus of subsequent simulated use testing. Note, it is often not possible to estimate the probability of occurrence for use errors, for the critical task performance, and it is necessary to evaluate the risk on the basis of the nature of the harm alone. Therefore, critical tasks that are performed infrequently should not be excluded from evaluation in HF-U testing and any task failures or difficulties found during testing should have a follow-up root cause analysis.

    f. A summative HF-U validation study based on simulated use of critical tasks, representing actual use. This study should evaluate a representative sample of 15 participants from each distinct user group. Upon completion of simulated use scenarios then subjective investigation of task specific performance can take place.

    g. HF-U validation study results should include performance data and subjective assessment regarding critical tasks. Performance data (task failures, close

calls or serious difficulties) must be identified as well as subjective data derived from interviews with test participants following simulated device use. Subjective assessment should include each test participant's perspective on the use of the device overall, any difficulties or confusion they experienced, and any of the tasks for which failure, close call, or difficulty occurred. Note that root cause evaluation should include specific consideration of this subjective assessment by test participants involved with the failures.

h. A conclusion regarding the adequacy of the design of the UI to support safe and effective use.

We recommend that you submit a draft HF-U validation testing protocol to the Agency for review prior to starting the testing. For more information, refer to the Agency's guidance document on human factors and particularly its relationship to risk management, available at https://www.fda.gov/media/80481/download.

Please note that this feedback applies to both the Mighty Medic and the Waterpipe device.

If we have additional comments or information requests not related to this clinical hold, we will notify you. Your responses to any non-hold issues should be addressed in a separate amendment to the IND.

If you have any questions, contact Iram Baig, Regulatory Project Manager, at [redacted]

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, MD
Director
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

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/

TIFFANY R FARCHIONE
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