IND 110513

CONTINUE PARTIAL CLINICAL HOLD

Multidisciplinary Association for Psychedelic Studies (MAPS)
Attention: Shannon DiNapoli
Head of Global Regulatory
3141 Stevens Creek Blvd #40563
San Jose, CA 95117

Dear Ms. DiNapoli:

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, that provide a response to our May 10, June 3, and December 27, 2021, 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): Insufficient information to assess risks to human subjects

CHEMISTRY MANUFACTURING AND CONTROLS

1. With respect to the 0.5 gram pre-rolled cigarettes:

    a. You must provide a certificate of analysis (CofA) for the cigarettes to be used in the clinical study showing testing for all cannabinoids present and terpenes to 100% mass balance, pesticides, elemental impurities, mycotoxins, and microbiological testing.

    b. You must provide stability data for the cigarettes in the packaging that the study participants will be using to store their cigarettes during the trial; typically, at least 30 days of stability data is provided. (You should update stability data as it becomes available for the length of the trial.)

These requirements may be satisfied by obtaining, and submitting, a letter of authorization to reference an existing IND, NDA, or supplier's drug master file (DMF) that contains the required information.

2. We note a CofA for placebo cannabis lot 1004-1904-01 was provided in your August 16, 2022, submission (SN 0023). You must provide mycotoxins and updated microbiological testing for this material.

CLINICAL

1. You have not provided adequate data to support the safety of the proposed dose of cannabis with high THC for use as directed in the amended protocol. To resolve this deficiency, you must characterize the safety, tolerability, and pharmacokinetics of the proposed dose and dose regimen of your cannabis product with high THC.

2. You have not provided data to support the safety of the proposed mode of administration (inhalation via smoking or water pipe or vaporizer) of your cannabis product with high THC. The pharmacokinetic studies you submitted are not adequate to inform the safety of the proposed dose with each delivery method. To resolve this deficiency, you must characterize the safety, tolerability, and pharmacokinetics of the different routes of administration/delivery methods and generate data to support their interchangeability.

3. Self-titration is not an acceptable dosing regimen, and it is not an acceptable risk mitigation strategy (see the Continue Partial Hold letter dated December 27, 2021).

4. The safety of exposing cannabis naïve participants to your cannabis product with high THC is unknown. To resolve this deficiency, you must characterize the safety and tolerability of your cannabis product with high THC in cannabis naïve subjects.

5. You state in your information request response that you intend to use the vaporization device, Mighty Medic, manufactured by Storz and Bickel, as well as the waterpipe device, Eyce Beaker, manufactured by Eyce Molds, for your study. You have not provided supporting information to demonstrate safety of these devices. You have not provided a device description, intended use, risk-benefit analysis, or validation/verification testing. You must provide detailed information for each of your devices for the Agency to review whether they pose undue risks to the patients of your proposed study; see the Center for Devices and Radiological Health, Office of Product Evaluation and Quality, list of requirements attached to this letter. Alternatively, you can provide a Letter of Authorization for an appropriate Device Master File, with descriptions of where relevant safety information can be located.

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 remind you of the non-hold issues in our May 10 and June 3, 2021, letters. In addition, we have the following additional recommendations and requests that are not clinical hold issues. Your responses to any non-hold issues should be addressed in a separate amendment to the IND.

CHEMISTRY, MANUFACTURING, AND CONTROLS

Microbiology

Your response that the acceptance criteria listed in Table 2 *Recommended Microbial Limits for Botanical Ingredients and Products-Dried or Powdered Botanicals* of USP <2023> are being used because the *Cannabis and Cannabis-derived Compounds* guidance defines cannabis as a botanical raw material, botanical drug substance, or botanical drug product is acknowledged. However, your assumptions are not correct. Table 2 of USP <2032> *Microbiological Attributes of Nonsterile Nutritional and Dietary Supplements* applies specifically to *raw materials, pharmaceutical ingredients, and active ingredients used in the manufacture of nutritional and dietary articles….* Cannabis used in clinical trials, although botanical material, is considered a drug product and not a nutritional or dietary article. The recommendations for testing and acceptance criteria for the cannabis products used in your studies should be derived from Table 1 of USP <1111> *Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use*. Therefore, work with your supplier to revise the cannabis drug product and cannabis placebo final specifications to reflect the microbiological testing acceptance criteria for Total Aerobic Microbial Count (TAMC) and Total Yeast and Mold Count (TYMC) as defined in USP <1111> *Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use* for non-sterile, non-aqueous inhaled drug products.

CLINICAL

1. We strongly recommend that you request a Type A meeting prior to submit another response to hold, to discuss your development program.

2. You may consider conducting a phase 1 dose escalating study to evaluate safety, tolerability and pharmacokinetic of different dosages, dose regimens and routes of administration to inform your phase 2 study protocol design.

3. Additionally, we have the following non-hold comments referred to the current version of protocol MJP2:

    - 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.

    - You should add assessment of vital signs at every face-to-face visit.

    - A physician should be within 15 minutes of the study site.

    - You should clarify the exact dose intended to be administered in the introductory session.

If you have any questions, contact Iram Baig, Regulatory Project Manager, at Iram.Baig@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

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. 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.

    e. 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.

    f. 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.

g. 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; and

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 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 to 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.

It is recommended 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.

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/

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