IND 110513

MEETING MINUTES

Multidisciplinary Association for Psychedelic Studies (MAPS)
Attention: Rick Doblin, PhD
Founder and President
3141 Stevens Creek Blvd. #40563
San Jose, CA 9511

Dear Dr. Doblin:[1]

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*.

We also refer to the meeting between representatives of your firm and the FDA on June 15, 2023. The purpose of the meeting was to gain agreement from the Agency on the sufficiency of the safety information to support the proposed dosing paradigm, proposed administration instructions, and inclusion of cannabis-naïve participants.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Enclosure:

- Meeting Minutes

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: A
Meeting Category: Guidance

Meeting Date and Time: June 15, 2023, 11:00 a.m. to 12:00 p.m. (EDT)
Meeting Location: Hybrid (In-person and Zoom.Gov)

[redacted]

Application Number: 110513
Product Name: Marijuana, *Cannabis sativa*
Indication: Posttraumatic stress disorder (PTSD)
Sponsor Name: Multidisciplinary Association for Psychedelic Studies (MAPS)
Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Tiffany Farchione, MD
Meeting Recorder: Valerie Magda, PharmD

FDA ATTENDEES

Teresa Buracchio, MD	Director (acting), Office of Neuroscience
Tiffany R. Farchione, MD	Director, Division of Psychiatry (DP)
Valentina Mantua, MD	Clinical Team Lead, DP
Ikram Elayan, PhD	Pharmacology/Toxicology Supervisor, Division of Pharmacology and Toxicology for Neuroscience (DPT-N)
Antonia Dow, PhD	Pharmacology/Toxicology Team Lead, DPT-N
Yongbin Zhang, PhD	Pharmacology/Toxicology Reviewer, DPT-N
Venkateswaran ChithambaramPillai, PhD	Clinical Pharmacology Team Leader (acting), Office of Clinical Pharmacology (OCP)
Kofi Kumi, PhD	Clinical Pharmacology Reviewer, OCP
Peiling Yang, PhD	Biometrics Team Leader, Office of Biostatistics (OB)
Kelly Yang, PhD	Biometrics Reviewer, OB
Charles Wu, PhD	Botanical Review Team Lead, Office of Pharmaceutical Quality (OPQ)
Eric Bow, PhD	Drug Product Reviewer, OPQ
Valerie Magda, PharmD	Regulatory Project Manager, Division of Regulatory Operations for Neuroscience-Psychiatry Group
Tyler Osselborn	Pharmacy Student

SPONSOR ATTENDEES

Rick Doblin, PhD	Founder and President, MAPS
Allison Coker, PhD	Program Manager, MAPS
Josephine Torrente	Director, Hyman Phelps & McNamara, PC
Suzanne Sisley, MD	President, Scottsdale Research Institute
Anton Harb Jr.	Iraqi War Veteran, Michigan Cannabis Regulatory Agency
Charleen Justice	Executive Manager

1.0 BACKGROUND

The Sponsor has been conducting clinical trials of whole plant marijuana (cannabis) for treatment of posttraumatic stress disorder (PTSD) under IND 110513 since 2010. As per the Sponsor, "given the increasing prevalence of self-administration of cannabis among US military veterans with PTSD, there is strong public interest in scientific data assessing whether self-administration of whole plant cannabis may be an effective treatment for this indication."

The Sponsor completed Study MJP1, a randomized, placebo-controlled, double-blind pilot in 76 veterans with PTSD, which tested three formulations of combusted cannabis—each with a different concentration of cannabinoids (e.g., THC, CBD)—versus placebo. The study did not meet its primary endpoint (the group treated with the highest concentration of cannabinoids did not separate from placebo on the Clinician Administered PTSD Scale). The Sponsor considers this finding to be due to the lack of statistical power and, therefore, has planned a larger study.

MJP2 would be a larger (N=320), multicenter, randomized, placebo-controlled, double-blind parallel-arm study to assess the safety and efficacy of inhaled cannabis (from cigarettes or from a vaporizer) compared to placebo. The active arm would have a THC concentration ranging from 15% to 25% and the placebo would be cannabis with a THC concentration <1%). The total daily amount of cannabis exposure is calculated to be up to 3 g/day per participant.

Study MJP2 was placed on clinical hold on May 10, 2021, because the Sponsor had not provided sufficient data to assess the risk of the proposed dose of cannabis under conditions of maximum use (e.g., 3 g within a single 60-minute daily session via vaporization). A Complete Response to Hold was submitted on November 29, 2021, and the Sponsor proposed to decrease the daily maximum dose of cannabis from 3 g/day to 2 g/day. The Division continued the partial hold and highlighted the lack of clinical and clinical pharmacology information to assess the safety of the proposed cannabis dose containing high THC concentrations (25%), which could have delivered up to 500 mg of THC/day under a scenario of maximum use. The Continue Partial Hold letter included botanical, microbiology, and drug product deficiencies as well as the safety concern regarding using smoked cannabis as a delivery method.

To resolve the deficiencies, the Division required that the Sponsor: 1) modify the proposed maximum possible dose or provide scientific evidence that supports the safety of the currently proposed maximum dose; 2) change the route of administration to a route without the safety concerns of smoking or provide scientific evidence that the proposed routes of administration do not place the participants (who may not have had a history of smoked or vaped cannabis) at undue risk.

In response, the Sponsor did not change the protocol substantially; *ad libitum* daily self-administration of inhaled cannabis with high THC (20.0% ± 3.0%) was still allowed with any preferred mean, either via a vaporizer, a pipe, or pre-rolled cigarettes. The study continued to allow enrollment of drug naïve subjects.

In a Continue Partial Hold letter issued on December 16, 2022, the Division concluded that the Sponsor had not provided sufficient data to support the safety of the proposed dose of cannabis with high THC for use as directed in the amended protocol and that the Sponsor had not provided either clinical or pharmacokinetic data to support the safety of the proposed mode of administration (inhalation via smoking, water pipe, or vaporizer). The letter reiterated that self-titration is not an acceptable dosing regimen or risk mitigation strategy and that the safety of exposing cannabis naïve participants to cannabis product with high THC was not established. Other hold issues were related to the vaporization device, and to the lack of the certificate of analysis (CofA) and stability data for the cigarettes.

The Sponsor's stated objectives for this Type A meeting are to discuss the Clinical Hold for Study MJP2 to address the protocol's deficiencies. Specifically, the Sponsor hopes to gain agreement from the Agency on the sufficiency of the safety information to support the:

- Proposed dosing paradigm
- Proposed administration instructions
- Inclusion of cannabis-naïve participants

FDA sent Preliminary Comments to MAPS on June 9, 2023.

2.0 DISCUSSION

2.1. CLINICAL

Question 1: Does the Division agree that the removal of the additional administration devices and methods of administration resolves the clinical hold issue related to the administration methods?

FDA Response to Question 1: *If you remove the vaporization device, Mighty Medic (manufactured by Storz and Bickel) and the waterpipe device, Eyce Beaker (manufactured by Eyce Molds) from the protocol, you are no longer required to provide supporting information to demonstrate safety of these devices. This resolves hold issue 5 of the Continue Partial Clinical Hold letter dated December 16, 2022. However, you have not resolved hold issue 2 related to the method of administration. You have not characterized the safety, tolerability, and pharmacokinetics of smoking as a mode of administration. Smoking is not a safe drug delivery system. Literature on short-term cannabis effect on pulmonary system is conflicting and we continue to have concerns that the protocol utilizes a harmful drug delivery system. We acknowledge our communication dated September 2, 2015, which allowed your pilot Study MPJ1 to proceed with smoking as a drug delivery system; however, the Division does not currently allow smoking as a drug delivery method for reasons of safety as well as data interpretability.*

> ***Discussion:*** *The Sponsor informed the Agency that this protocol has been transferred to their research branch and it is no longer intended to support commercial development. The Sponsor committed to submitting this information to the IND. The Sponsor further clarified that the objective of this protocol has shifted from drug development to a research study to investigate safety and real-world effectiveness of cannabis use in veterans affected with PTSD. Therefore, the the protocol seeks to utilize a cannabis delivery method which reflects real-world cannabis use. The Sponsor asked if, given this context, the Agency had specific safety concerns with either smoking or vaping. The Agency clarified that there are pulmonary safety concerns related to smoking as well as vaping. The Division of Pulmonology, Allergy and Critical Care (DPACC) will provide additional guidance in a separate post-meeting communication to help the Sponsor select the most appropriate method. The Agency reiterated the comments outlined in the Continue Partial Clinical Hold letter dated December 16, 2022, related to the devices.*

Question 2: Does the Division agree that the Sponsor has provided sufficient information to support the safety of smoking 2.0 grams of 20% ± 2% THC-cannabis per day, with dosing limited to no more than of 1.0 gram per any 6-hour period in Study MJP2?

FDA Response to Question 2: *We do not agree that you provided sufficient information to support the safety of smoking 2 gr/day of cannabis with 20 ± 2% THC content (approximately 400 mg/day of THC). In relation to the maximum daily dose of THC, we reiterate that in Study MJP1 the dose was 1.8 g/day with a lower concentration of THC (12.4%) and that in Study MJP2 you intend to administer up to 2 g/day of cannabis with a higher THC concentration (up to 22%).*

We acknowledge the published paper by Ware et al. (2022) related to cannabis use for management of pain in non-cancer patients. The Study provides preliminary clinical

safety information for that population; however, the study design (prospective cohort study) does not allow a throughout understanding of the safety of the daily THC dose that you propose for your study.

To address this issue, we recommend conducting a phase 1 dose-escalation study to evaluate the safety, tolerability, and pharmacokinetic profile of different dosages and dose regimens (administered via a safe delivery method) to inform your phase 2 study protocol design.

> ***Discussion:*** *Agency agreed with the Sponsor's proposal to limit the amount of cannabis use in a given time (6 hours), but clarified that the maximum daily dose of THC would need to be justified. The Agency also clarified that a maximum daily dose of cannabis of 1.8 g/day with a lower concentration of THC (12.4%) as that utilized in Study MJP1 would be acceptable. The Sponsor further clarified that they intend to use a cannabis formulation with a higher than 12.4% THC concentration in order to minimize the amount of smoking. The Agency expressed openness to accept a maximum daily THC dose higher than that used in protocol MPJ1 if adequately justified. The Sponsor committed to submitting an amended protocol with a proposal for a new dose and its justification.*

Question 3: In the context of this research IND and the changes in maximum THC dose, does the Division agree that self-titration is an acceptable dosing strategy for Study MJP2?

FDA Response to Question 3: *We reiterate that self-titration is not an acceptable dosing strategy for Study MJP2. In addition to not being an acceptable risk mitigation strategy, self-titration will render the data uninterpretable in relation to dosing, efficacy, and safety outcomes. A protocol that includes self-titration would be considered clearly deficient in design to meet its stated objectives (grounds for imposition of clinical hold as per 21 CFR 312.42(b)(2)(ii)).*

> ***Discussion:*** *Following the Sponsor clarification that the MPJ2 protocol will no longer be intended as a phase 2 study in support of a future marketing application, the Agency expressed openness to accepting self-titration as a dose regimen. However, the Sponsor must first find agreement with the Agency on the maximum daily dose of THC allowed in the protocol and must not use self-titration as a risk minimization strategy. The Agency reiterates that self-titration limits data interpretability related to both efficacy and safety; however, shifting the scope of the study to a research protocol which aims at collecting descriptive data on real-world cannabis use mitigates the Agency's concerns.*

Question 4: Does the Division agree that Study MJP2 may enroll participants with all levels of cannabis experience, including cannabis-naïve subjects?

FDA Response to Question 4: *We do not agree that MJP2 may enroll cannabis-naïve participants. Literature on short-term cannabis effect on pulmonary system is conflicting and concerns that the protocol utilizes a harmful drug delivery system continue, especially in subjects with no history of exposure to the risks of smoking. As stated in the Partial Hold Letter, "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" (see our response to Question 2 for a recommendation on addressing this issue).*

Cannabis-naïve subjects may be included only after safety, tolerability, and pharmacokinetic profile of different dosages and dose regimens (administered via a safe delivery method) have been well characterized.

> ***Discussion:*** *DPACC will provide additional guidance on the safety of smoking in naïve subjects in a separate post-meeting communication to help the Sponsor select the most appropriate patient population. The Agency reiterated that cannabis-naïve subjects may be included only after safety and tolerability have been established. The Sponsor should include a proposal for assessing safety and tolerability in cannabis-naïve subjects in the amended protocol which will be submitted to the IND.*

3.0 OTHER

SECURE EMAIL

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or subject information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to [redacted]. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

ADDITIONAL IND RESPONSIBILITIES

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available online for your convenience.[2] Your responsibilities include:

[2] https://www.ecfr.gov/cgi-bin/text-idx?SID=3ee286332416f26a91d9e6d786a604ab&mc=true&tpl=/ecfrbrowse/Title21/21tab_02.tpl

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. Submit 15-day reports to FDA electronically in eCTD format via the ESG.

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND became active (the date clinical studies were permitted to begin) [21 CFR 312.33].

SUBMISSION REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information, visit FDA.gov.[3]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*.[4]

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs, and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[5]

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[3] http://www.fda.gov/ectd
[4] https://www.fda.gov/drugs/forms-submission-requirements/electronic-regulatory-submission-and-review
[5] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,[6] as well as email access to the eData Team [redacted] for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[7] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.[8] For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of

[6] https://www.fda.gov/media/88173/download
[7] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[8] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide[9] (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.[10] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[11]

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources.[12]

PEDIATRIC ASSESSMENTS

As amended by the Food and Drug Administration Safety and Innovation Act (Public Law 112-144, 126 Stat. 993) of July 9, 2012, the Pediatric Research Equity Act (PREA) requires any sponsor who plans to file a marketing application for a drug or biological product (FDCA section 505 or PHSA section 351, respectively) that includes a new active ingredient, new indication, new dosage form, new dosing regimen, and/or new route of administration to submit an initial Pediatric Study Plan (PSP; 21 U.S.C. 355c). The intent of the PSP is to identify needed pediatric studies and begin planning for these studies. The timing and content of an initial PSP, including a template, can be

[9] https://www.fda.gov/media/88173/download
[10] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[11] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[12] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

found in the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans*.[13]. Review this guidance and the PREA requirements to determine if your application must contain an assessment (pediatric clinical data), waiver request, and/or deferral request (21 U.S.C. 355c).

If you have any questions, you may contact the Division of Pediatric and Maternal Health at [redacted] or email [redacted].

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

Agency to send DPACC comments.

6.0 ATTACHMENTS AND HANDOUTS

None.

[13] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended

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/s/

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