IND 110513

ADVICE/INFORMATION REQUEST

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 Agency's final meeting minutes dated July 12, 2023, stating that Division of Pulmonology, Allergy, and Critical Care (DPACC) would provide additional guidance on the safety of smoking in naïve subjects in a separate post-meeting communication.

The following comments and recommendations supplement FDA responses enclosed in the Type A meeting minutes dated July 12, 2023:

1) Regarding pulmonary safety of pre-rolled cigarettes as a cannabis delivery method:

   Available data suggest that smoke is harmful to lung health regardless of the source (e.g., burning wood, tobacco), and this includes marijuana. For example, marijuana smoke contains about 50% more benzopyrene and nearly 75% more benzanthracene – both polycyclic aromatic hydrocarbon procarcinogens – than the smoke from a comparable quantity of unfiltered Kentucky reference tobacco cigarettes. Marijuana smoke also contains other carcinogens and cocarcinogens found in tobacco smoke, including phenols, vinyl chlorides, nitrosamines, and reactive oxygen species (Tashkin, 2013). The literature suggests that differences in the technique of smoking marijuana compared with tobacco – including deeper inhalation and longer breath-holding time – result in a four-fold increase in deposition of the tar from marijuana compared to an equivalent amount of tobacco (Hancox et al., 2010). The loosely- packed nature of cannabis joints – resulting in less rod filtration and promoting hotter combustion – as well as the absence of a filter tip contribute to a substantially greater respiratory burden of carbon monoxide and tar compared to tobacco smoking (Wu et al., 1988). In summary, combustion of marijuana in a cigarette can amplify exposure of the lung to the carcinogens within the smoke. Several studies have demonstrated that habitual cannabis smoking results in a high frequency of cough, sputum, and wheezing (Hancox et al. 2015).

[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.

The available evidence demonstrates that pre-rolled cigarettes as a cannabis delivery method is harmful to the lungs.

2) Regarding pulmonary safety of vaping (via inhaler or pipe) as a cannabis delivery method:

Although vaping is often considered safer than smoking combusted particles, vaping is still harmful to the lungs, and the full effects of vaping on the respiratory system are active areas of investigation. Vaping may result in e-cigarette or vaping product use-associated lung injury (EVALI)—a potentially serious or even life-threatening form of acute lung injury. EVALI often presents with shortness of breath, cough, wheezing, and chest pain. The types of lung injury observed in EVALI are heterogenous. The literature describes radiographic and histologic evidence of acute eosinophilic pneumonia, diffuse alveolar damage, organizing pneumonia, and lipoid pneumonia (Layden et al. 2019). The majority of EVALI cases reported are associated with the vaping of THC-containing products. Analyses by the FDA and the CDC identified the association between vitamin E acetate and EVALI (Blount et al. 2019). Vitamin E acetate is used as a thickening agent in THC products. When inhaled, vitamin E is incorporated into the natural phospholipids that comprise surfactant, leading to a loss of normal functioning surfactant and causing an inflammatory cascade in lung tissue. The mechanisms by which inhaling electronic cigarette vapor causes lung injury are summarized in Figure 1. Therefore, there is substantial evidence that electronic cigarettes (with and without THC use) can lead to lung disease, and that vaping may lead to oxidative and inflammatory damage to the lungs. As for the pulmonary safety of smoking via a pipe, studies have shown that because classical cigarettes and pipes both involve combustion, similar toxic compounds are produced by both delivery methods. Like e-cigarette users, pipe users may take higher puff volumes and more frequent puffs and, thus, increase their exposure to toxicants.

Figure 1. Mechanisms of Lung Injury of Electronic Cigarettes

Product constituent	Mechanism of Lung Injury
General electronic cigarette vapor	-asthma, cough -histological damage -DNA damage -inflammatory changes -oxidative damage
Vitamin E acetate (contaminant)	-implicated in EVALI
Heating coil	-heavy metal toxicity
Wicking material	-silica content, silicosis
Flavoring	-thermal degradation -benzaldehyde -diacetyl
Propylene glycol, vegetable glycerin	-thermal degradation -formaldehyde -acetaldehyde -lipid content

Source Winnicka and Shenoy (2020)

3) Regarding whether the risk changes depending if subjects were previous tobacco smokers:

   EVALI is a clinical diagnosis that requires the use of an e-cigarette in the 90 days preceding the appearance of initial symptoms; however, there is evidence suggesting that previous tobacco smokers who vape may develop symptoms of acute lung injury more quickly (i.e., within hours of vaping). In a literature review of multiple cases of EVALI with varying durations of product use before symptom development (ranging from a few hours to months), many of the cases with rapid onset were observed in former or current smokers. In one case study, a 41-year-old man who had been an asymptomatic daily cigarette smoker for 11 years, developed persistent cough and shortness of breath within a few hours of using an e-cigarette (Deliwala et al. 2020). While there is a need for more research measuring the risk of vaping in former tobacco smokers, current evidence suggests that e-cigarettes may pose a higher risk in former tobacco smokers.

4) Regarding whether the risk changes whether subjects were previous cannabis smokers:

   Similar to the scenario discussed above, there is a need for more research measuring the risk of inhaled cannabis in former cannabis smokers. Given the known pulmonary damage caused by vaping and inhaled cannabis separately, it is likely that e-cigarettes may pose a higher risk in former cannabis smokers.

5) Regarding if there are pre-existing conditions which are not compatible with smoking or vaping:

   The American Thoracic Society and the American Lung Association strongly recommend against smoking or vaping for anyone, but particularly in people with an existing lung disease, such as chronic obstructive pulmonary disease (COPD) or asthma.

We remind you that Protocol MJP2 is on Clinical Hold. Until you have submitted the required information described in our letter dated December 16, 2022, and we notify you that you may initiate the study, you may not legally conduct the study under this IND. Please submit your response to the clinical hold issues as described in the December 16, 2022, letter.

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:

- 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; and

- 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. The following submission types: **NDA, ANDA, BLA, Master File** and **Commercial INDs** must be submitted in eCTD format. 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*. For additional information, see FDA.gov.[4]

SECURE EMAIL

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential

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

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.

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.

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