Docket No. FDA-2020-D-1079-0001

Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research

Comment #1: Section III Part A: Sources of Cannabis
At this time the recommendations indicate that only cannabis and cannabis-derived products that contain less than 0.3% delta-9 THC be used for clinical research. The USDA has limited hemp production to ≤0.3% delta-9 THC with a proposed variability range based on measurement uncertainty of up to 0.5% delta-9 THC.

Americans for Safe Access recommends that FDA not limit the amount of delta-9 THC that may be present in clinical research products. The FDA has approved medications containing delta-9 THC (Appendices 1-2), indicating that FDA has determined that there is medical value to delta-9 THC and it has been shown to treat specific conditions including anorexia and nausea associated with chemotherapy and HIV/AIDS. FDA also understands that each patient is different and dosing should be determined based on the patient's medical need and not a pre-defined volume of THC per dose, as evidenced by the multiple dosages available in cannabinoid-based medicines currently approved by FDA (Appendices 1-3). Further, allowing for administration of a wider range of THC volumes in medical cannabis products will facilitate deeper research on the potential for cannabis to treat a greater variety of patient conditions, as well as address patient-to-patient variations in treatment applications.

According to a WHO study published in 2018, it was noted that the LD_{50} for rats and monkeys was high enough "that such a dose could not be realistically achieved in a human following oral consumption, smoking or vaporising the substance, as Δ9-THC has a large margin of safety"[1]. The US National Toxicology Program has also noted that "Δ 9 -THC does not have mutagenic or carcinogenic effects."[2] This high safety profile means that patients may start with low doses and increase as needed to continue to derive medical benefit from these products while still being safe with regard to more adverse side effects.

Comment #2: Section III Part B: Resources for Information on Quality Considerations
Americans for Safe Access agrees that products containing 0.3% delta-9 THC and CBD should be produced under the same good manufacturing practices as required for other IND's and NDA's in order to establish identity, purity, strength, quality, and safety. Americans for Safe Access urges FDA to require DEA to approve additional suppliers of research grade cannabis and cannabis-derived products. Americans for Safe Access will provide written comments to DEA which include the current comments submitted to FDA which will include our request to increase the number of approved suppliers of cannabis and cannabis-derived products.

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[1] World Health Organization Expert Committee on Drug Dependence Pre-Review (2018). Delta-9tetrahydrocannabinol. Section 3: Toxicology.

[2] National Toxicology, P., *NTP Toxicology and Carcinogenesis Studies of 1-Trans-Delta(9)- Tetrahydrocannabinol (CAS No. 1972-08-3) in F344 Rats and B6C3F1 Mice (Gavage Studies)*. Natl Toxicol Program Tech Rep Ser, 1996. **446**: p. 1-317.

ASA also encourages FDA to establish a clear delineation between products considered research grade and products approved for sale in states that have approved medical or adult-use cannabis programs. While these products should be manufactured to adhere to a specific standard, ideally those required for dietary supplements or food products, the conflict of laws between the federal and state governments regarding the classification of cannabis as a Schedule I drug under the Controlled Substances Act does not permit such a standard to be applied at this time. Without a clear delineation of products there may be confusion on the part of the consumer with respect to the standards that products were manufactured and tested to that they must adhere to.

Comment #3: Section III Part B: Resources for Information on Quality Considerations
Americans for Safe Access agrees that IND methods validation should follow the ICH guidance for industry Q2(R1) Validation of Analytical Procedures: Text and Methodology (March 1995). This method validation procedure contains robust and stringent acceptance criteria indicating that an analytical testing method is fit for purpose. While many groups are attempting to publish methods for quantitatively determining cannabinoid and terpenoid content, they are not requiring the analytical methods to have such a robust method validation.

Additionally, states that have specific requirements for cannabis testing laboratories often don't require as stringent a method validation as that from ICH. Many often stop at only requiring the laboratory to obtain ISO 17025 accreditation, where section 7.2.2.1 states "The laboratory shall validate non-standard methods, laboratory-developed methods and standard methods used outside their intended scope or otherwise modified. The validation shall be as extensive as necessary to meet the needs of the given application or field of application."[3] This leaves it open to interpretation by the laboratory which may opt to not conduct such a rigorous method validation.

[3] International Standards Organization (2017). International Standard ISO/IEC 17025:2017 General Requirements for the Competence of Testing and Calibration Laboratories.