Akamai Cannabis Clinic
3615 Harding Ave, Suite 304
Honolulu, HI 96816

May 28, 2019

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2019-N-1482 for "Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds; Public Hearing; Request for Comments."

Thank you for this opportunity to provide comments on the regulation of cannabis and cannabis-derived compounds, specifically cannabidiol (CBD). It is encouraging to see that the Food and Drug Administration (FDA) is taking additional steps to investigate the ongoing unbridled production and distribution of CBD products in the United States.

As a certifying physician for Hawaii's Medical Use of Cannabis Program, I am constantly faced with safety issues surrounding the medical use of cannabis by registered patients in our state. It is my goal to address what I see as the most important health concerns related to the current widespread availability of unregulated CBD products.

To begin, I would like to frame my comments within the broader context of the states' authority to accept the medical use of controlled substances.

In its notice of public hearing and request for comments pertaining to cannabis and cannabis-derived compounds, the FDA makes reference to state medical use of cannabis programs in the following manner:

"The legality of cannabis has been changing over time at both the State and Federal levels. Currently, 33 States and Washington, DC, allow "medical" use of marijuana under State law and 14 additional States have State law "medical" programs that are limited to CBD products."

Referring to state medical use of cannabis programs as "medical" programs, suggests that these state programs somehow fall short of legitimate medical use, and ignores the authority reserved to states under federalism to accept the medical use of controlled substances.

State medical use of a controlled substance is currently accepted medical use in treatment in the United States, which means that the federal regulation that has marihuana listed as a Schedule I controlled substance does not apply to the state medical use of cannabis.

We already have an example of where the specific use of a Schedule I controlled substance is exempt from federal regulation:

Exempt from federal Schedule I:
21 CFR 1307.31 - Native American Church.
"The listing of peyote as a controlled substance in Schedule I **does not apply** to the nondrug use of peyote in bona fide religious ceremonies of the Native American Church, and members of the Native American Church so using peyote are exempt from registration."

If a religion can enjoy an exemption from federal regulation for the specific use of a Schedule I controlled substance, then why can't a state?

There are also at least two other examples of cannabis exemptions for specific activities under state law and federal regulation:

Exempt from Guam Schedule I:
Section 2. The following *new* subsection (g) is added to Appendix A of Chapter 67 of Title 9 Guam Code Annotated, to read as follows:
"(g) The enumeration of marihuana, tetrahydrocannabinols or chemical derivatives of these as Schedule I controlled substances **does not apply** to the medical use of cannabis pursuant to the Joaquin Concepcion Compassionate Cannabis Use Act of 2013."

Exempt from the federal restriction on carriage aboard aircraft:

14 CFR 91.19 Carriage of narcotic drugs, marihuana, and depressant or stimulant drugs or substances.

"(a) Except as provided in paragraph (b) of this section, no person may operate a civil aircraft within the United States with knowledge that narcotic drugs, marihuana, and depressant or stimulant drugs or substances as defined in Federal or State statutes are carried in the aircraft.

(b) Paragraph (a) of this section **does not apply** to any carriage of narcotic drugs, marihuana, and depressant or stimulant drugs or substances authorized by or under any Federal or State statute or by any Federal or State agency."

It is important to realize the impact that the state-accepted medical use of cannabis has upon the federal Controlled Substances Act (CSA) when it comes to the state and federal regulation of controlled substances, because the authority of states to regulate the exclusively intra-state production and distribution of CBD apart from the FDA will also need to be included in this discussion.

Another issue that needs to be considered at the outset is the scheduling status of unapproved CBD.

Just because hemp has been removed from the federal CSA by the Agriculture Improvement Act of 2018 does not mean that cannabinoids found in hemp that are already approved drug products, or that are being investigated for medical use under a FDA Investigational New Drug (IND) application, can be isolated from hemp and marketed as unapproved drug substances. If this were the case, then delta-9-tetrahydrocannabinol (THC) found in hemp at 0.3% or less could be extracted, purified, and sold in unapproved form on the open market. Obviously, this would be illegal. Unapproved THC still resides in federal Schedule I.

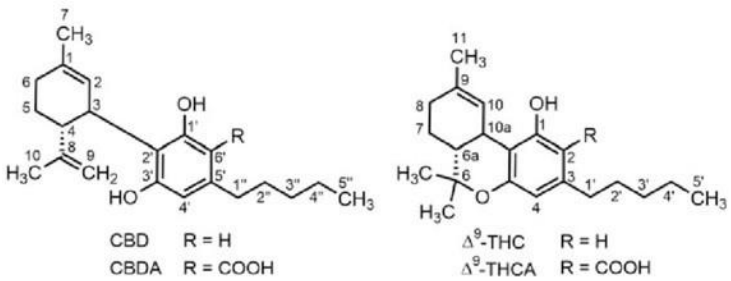
In addition, now that the very first botanically derived FDA-approved CBD oil has been placed in the least restrictive federal controlled substance schedule by the Drug Enforcement Administration (DEA), we must ask the question: If a CBD drug product that has successfully completed FDA clinical trials, and is being produced under strict GAP and GMP standards, is in federal Schedule V, which still requires a prescription from a healthcare provider with DEA controlled substance prescribing registration, then how can an unapproved CBD drug substance, with unproven safety and efficacy, that is produced under questionable conditions, be in a less restrictive schedule?

Furthermore, if we follow the federal definition of tetrahydrocannabinols, then it would also appear that unapproved CBD is a Schedule I controlled substance, because CBD is a derivative of THC:

21 CFR 1308.11(d):
(31) Tetrahydrocannabinols
"Meaning tetrahydrocannabinols naturally contained in the plant of the genus Cannabis (cannabis plant), as well as synthetic equivalents of the substances contained in the cannabis plant, or in the resinous extractives of such plant, and/or synthetic substances, derivatives, and their isomers with similar chemical structure and pharmacological activity to those substances contained in the plant …"

Various chemistry dictionaries define a derivative as a compound that can be imagined to arise or actually be synthesized from a parent compound by replacement of one atom with another atom or group of atoms.

The nearly identical chemical structures of THC and CBD make it possible to convert CBD into THC, and vice versa using relatively simple means:



Because CBD can be converted into THC, CBD can also be a source for illicit THC production.

And finally, there are three safety concerns pertaining to CBD that need to be addressed:

First, CBD has been shown to affect human Cytochrome P450 liver enzymes, which are responsible for the metabolism of a broad range of pharmaceutical prescription medications. This could be especially hazardous for patients who are being prescribed Coumadin, because taking CBD at the same time could potentially raise a patient's INR enough to cause dangerous internal bleeding. One study found that as little as 25 mg of CBD can impact human P450 function.

Unfortunately, all of the unregulated Hemp CBD products that we have seen on the market have been devoid of any warnings about potential drug interactions, and most do not provide third party laboratory testing for heavy metals and pesticides. This is a serious concern given hemp's known phytoremediation properties.

Second, the clinical studies conducted for FDA approval of Epidiolex demonstrated that CBD is not without adverse reactions:

"The most common adverse reactions (10% or more for EPIDIOLEX and greater than placebo) are: somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor quality sleep; and infections."

And third, a recent pre-clinical study found that topically applied CBD can elevate intraocular pressure (IOP) in mice, a finding that could negatively impact state medical use of cannabis patients who are using CBD products to treat their Glaucoma. Because the FDA clinical trials for Epidiolex did not follow IOP as an outcome measure, more research in this area is needed before the general commercialization of CBD is allowed.

Clearly, the FDA has several critical issues that it needs to address in order to make well-informed decisions about how to handle the current explosion of CBD snake oils. The so-called "CBD Industry" knows that the federal government is slow to act, which highlights the need for clear guidance regarding the FDA's position on unapproved CBD, and effective enforcement to ensure that our patients will be properly protected.

However, no matter what the FDA decides, it is still up to the states to determine how to regulate the intra-state production and distribution of their own CBD products. States have a unique opportunity to produce quality CBD products for medical use within their own state, but only if they recognize their authority to do so, and only if they can muster the political will necessary to promote locally sustainable healthcare.

Sincerely,

Clifton Otto, MD
3615 Harding Ave, Suite 304
Honolulu, HI 96816
808-233-8267.