April 23, 2018

Dockets for Management Staff (HFA-305)
Food and Drug Administration

5630 Fishers Lane, Rm. 1061

Rockville, MD 20852

Re: Docket No. FDA-2018-N-1072

International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; Cannabis Plant and Resin; Extracts and Tinctures of Cannabis; Delta-9-Tetrahydrocannabinol (THC); Stereoisomers of THC; Cannabidiol; Request for Comments

Dear Madam or Sir:

The American Botanical Council appreciates the opportunity to comment to the U.S. Food and Drug Administration (FDA) with regard to the medical usefulness and impact of scheduling changes on the availability for medical use of cannabis (*Cannabis sativa*, and presumably other species in the genus *Cannabis*, i.e., *C. indica*) and cannabis-derived substances. This is for the consideration in preparation of a response from the United States to the World Health Organization (WHO) regarding the abuse liability and diversion of these drugs.

Based on what clinical research and numerous case studies indicate as the promising medical benefits of cannabis as a medicine, we recommend that cannabis be taken off Schedule I of the Controlled Substances Act in the U.S. to allow for more thorough investigation of its therapeutic potential.

The American Botanical Council (ABC) is an independent, nonprofit, tax-exempt (under section 501(c)(3) of the Internal Revenue Code) research and education organization in Austin, Texas. ABC's membership includes medicinal plant researchers, health professionals, industry members, libraries, research centers, consumers, and other parties interested in medicinal plant research and education in approximately 80 countries. ABC publishes peer-reviewed publications which have included articles on various aspects of botanical and medical research on cannabis.

Current situation

As the agency is aware, the Controlled Substances Act of 1970 (21 U.S.C. 13 §801 et. seq) in the United States defines five classes of controlled substances, from I (most restrictive) to V (least restrictive). ABC holds the opinion that current scientific and clinical evidence supports the

position that cannabis is currently inappropriately listed as a schedule I ingredient. US Code 812 (b) defines ingredients in schedule I as those having the following attributes:

(A) The drug or other substance has a high potential for abuse.
(B) The drug or other substance has no currently accepted medical use in treatment in the United States.
(C) There is a lack of accepted safety for use of the drug or other substance under medical supervision

In 1970, when the Controlled Substances Act was enacted, reliable information on the medical value of cannabis was relatively scarce. This has changed over the past years, where a number of clinical studies have been carried out to evaluate cannabis, and cannabis isolates, for a variety of conditions and ailments (see below). ABC believes that more clinical and other research into the medicinal properties of cannabis is warranted, and that the schedule 1 status of cannabis is one of the most significant impediments to carry out such research. To obtain legal cannabis supplies for studies, researchers must get an approved IND application from the FDA, and get the investigator and research site registered by the DEA. In addition, the cannabis has to be obtained through NIDA, which still uses the University of Mississippi as the only federally-approved source that is allowed to legally grow cannabis for government-approved research studies. But even the University of Mississippi cannot import or conduct research on new chemovars obtained by selective breeding. This limits the availability of cannabis products of a particular composition (e.g., high-THC chemovars) for inclusion in modern research in the U.S.

Medicinal value of cannabis for selected conditions and diseases

Cannabis and Pain

There have been numerous studies investigating the effects of cannabis in patients with pain. A systematic review from 2017 concluded that “From 27 chronic pain trials, there is low-strength evidence that cannabis alleviates neuropathic pain but insufficient evidence in other pain populations.”[1] In an overview of systematic reviews and observational studies, Häuser et al. concluded that “sufficient evidence is available for neuropathic pain. A meta-analysis based on individual patient data on the use of medical marijuana to treat neuropathic pain found a NNTB [number needed to treat for an additional benefit] of 6 for pain relief of at least 30%. This finding meets the criteria for a clinically relevant benefit.”[2] Other systematic reviews have supported the benefits of cannabis preparations in neuropathic pain, but have determined that available clinical data are too limited to recommend cannabis treatment for other types of pain.[3,4]

Cannabis and Epilepsy

Systematic reviews on the benefits of cannabis preparations in patients with seizures are lacking, despite evidence that such use is not uncommon.[5] The majority of patient and caregiver surveys found either beneficial effects or no significant effect of cannabis in patients with epilepsy.[5] A review of the literature showed that clinical trials have been carried out primarily

with cannabinoids, for which efficacy is established.[6-9] In the review published by Stockings et al., the authors write "Pharmaceutical-grade CBD [cannabidiol] as adjuvant treatment in pediatric-onset drug-resistant epilepsy may reduce seizure frequency. Existing RCT evidence is mostly in pediatric samples with rare and severe epilepsy syndromes; RCTs examining other syndromes and cannabinoids are needed."[10] Evidence from parental reporting in patients using oral cannabis extracts suggests that such use is not uncommon, and 33% reported a greater than 50% reduction in seizures (responders). According to the authors of this study, the response rate is considered similar to placebo.[11] As explained above, there is evidence for the efficacy of CBD from a number of clinical studies, and on April 19, 2018, an FDA advisory panel on Thursday voted unanimously to recommend approval of a concentrated CBD extract to treat seizures caused by Lennox-Gastaut and Dravet syndromes.[12] The two conditions usually emerge in childhood and cause frequent, drug-resistant seizures.

Cannabis and Multiple Sclerosis

Similar to the case with epilepsy, there are no systematic reviews on the benefits of cannabis smoking or ingestion in multiple sclerosis. The data from clinical studies were predominantly carried out with purified extracts or cannabinoids, which, according to a systematic review from 2018, "find cannabinoids may have modest effects in MS for pain or spasticity."[13] Other systematic reviews suggest moderate evidence for a decrease in spasticity and spasm frequency in multiple sclerosis patients using cannabinoids, and improvements in cognitive function and ability to perform daily activities.[14] However, a review of the effects of a proprietary cannabinoid extract (Sativex®) suggests that "Efficacy of THC-CBD oromucosal spray has been proven in randomized, controlled clinical studies and its effectiveness confirmed in observational studies. It shows alleviation of symptoms together with improvement of daily activities and improvement in QoL [quality of life] for patients: approximately every second patient can benefit to achieve a relevant reduction of spasticity."[15] This particular cannabis extract is approved in 29 countries to treat spasticity in multiple sclerosis patients.

However, a systematic review of cannabis in the treatment of dystonia, dyskinesia, and tics reported that "the careful observations reviewed above lead to the conclusion that there is a direct effect of cannabis in various formulations in some conditions, especially hyperkinetic symptoms." In addition, a clinical study assessing the occurrence and severity of muscle spasms in 279 patients using a cannabis extract or placebo showed that 29.4% of subjects treated with the cannabis extract experienced significant stiffness relief compared to 15.7% using placebo. Combining this with the beneficial effects of the active drug on body pain, spasms and sleep quality, the results were considered as an indication of the effectiveness of the cannabis extract in treating symptoms of muscle stiffness in MS patients.[16]

Conclusion

Based on the available medical and scientific literature, it seems clear that attribute (B) of ingredients listed on schedule I of the Controlled Substances Act no longer applies to cannabis. The beneficial effects of cannabis in neuropathic pain are well-established. The efficacy of smoking or ingesting cannabis in other areas of therapeutic importance, such as epilepsy and multiple sclerosis, is currently not supported by sufficiently powered clinical data. However,

there is ample evidence for the therapeutic potential of purified cannabis fractions in these therapeutic areas. An urgent need exists to find new therapies for diseases such as epilepsy, which affects 2.9 million people in the U.S.[17] Nearly a quarter of patients remain resistant to drug therapy, failing to achieve sustained seizure freedom after use of two or more appropriately used antiepileptic drugs.[18] Based on the promising results from the human studies on cannabis, the current hurdles to investigate cannabis, cannabis extracts, and purified fractions obtained from cannabis, as promising ingredients for a number of medical issues do not seem appropriate in view of the potential benefits that this plant might provide. Therefore, the American Botanical Council recommends that cannabis be removed from Schedule I from the Controlled Substances Act and that other appropriate actions are undertaken to enable more appropriate access of cannabis and its components for medicinal investigations. (We have provided the cited literature below in References.)

We thank you for your consideration of these comments.

Respectfully,

Stefan Gafner, PhD
Chief Science Officer
American Botanical Council

[References on next pages]

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