WHO Expert Committee on Drug Dependence Critical Review:

Cannabidiol (CBD)

Expert Peer Review 2

1. Comments based on the review report

a. Evidence on dependence and abuse potential

Dependence potential:

The review could not identify studies regarding the potential physical dependence effects of CBD in laboratory animals nor human subjects. Regarding the possibility that CBD can produce a THC-like effect, the review indicates "...there is no evidence of that oral CBD administration in humans results in clinically relevant THC-like subjective or physiological effects, or appreciable plasma concentrations of THC or its metabolites."

Abuse potential:

CBD does not appear to act directly at cannabinoid CB_1 receptors; the receptor thought by many to mediate the abuse-related effects of cannabis. Additionally, it does not produce THC-like effects in the mouse tetrad assay. Generally, the effects of CBD do not indicate the likelihood of abuse in preclinical studies in that: it elevates intracranial-self-stimulation thresholds; it does not increase dopamine release in the mesolimbic ventral tegmental area-nucleus accumbens pathway; it does not induce conditioned place preference; nor does it generalize to the THC-discriminative stimulus in rats or pigeons.

In human experimental studies the review indicates that "While the number of studies is limited, the evidence from well controlled human experimental research indicates that CBD is not associated with abuse potential." It appears that the evidence for this is limited to two well-controlled studies. In one study, 600 mg of CBD given orally did not produce effects different from placebo in healthy subjects

on the Addiction Research Center Inventory (ARC). In a randomized, double-blind study using cannabis smokers, CBD administered by itself up to 800 mg p.o. produced no significant psychoactive, cardiovascular or other effects and was without abuse-related indicators in a variety of tests.

b. Risks to individual and society because of misuse

The review indicates that CBD has been found to have relatively low toxicity, although it also indicates that not all potential effects have been explored. None of the toxic effects specifically identified in the review appeared particularly troublesome. Adverse events reported in clinical studies investigating the therapeutic possibilities of CBD included, but were not limited to, somnolence, decreased appetite, diarrhoea, and fatigue.

c. Magnitude of the problem in countries (misuse, illicit production, smuggling etc)

The review indicates that "At present no public health problems (e.g., driving under the influence of drugs cases, comorbidities) have been associated with the use of pure CBD." In addition, the review indicates that there were no published statistics on seizures of illicit CBD available. There is, however, unsanctioned medical use of CBD-based products that are distributed in a variety of forms for a variety of ailments from cancer to PTSD.

At the time of this peer review (20180517), Annex data from country surveys were not available for comment.

d. Need of the substance for medical (including veterinary) practice

Cannabidiol is not listed on the WHO Model List of Essential Medicines (20th List) or the WHO Model List of Essential Medicines for Children (6th List). CBD is presently marketed in several countries in combination with THC in a 1:1 ratio (Sativex®). The review, however, indicates that "Currently there are no approved marketed pure CBD medicinal products, although several are in development."

CBD is in development for a variety of therapeutic applications including schizophrenia, Fragile X syndrome, encephalopathies, childhood absence seizures, Neonatal Hypoxic-Ischemic Encephalopathy (NHIE), and perinatal asphyxia. CBD appears most established for epilepsy. It is important to note that CBD has been

found effective in clinical studies of Lennox-Gastaut and Dravet syndromes that are resistant to other forms of medication; this observation may identify a therapeutic use of CBD for an under-served patient population.

Future studies should address the possibility that the metabolites of CBD are responsible for evidence of therapeutic effects, and not CBD (the parent) itself (e.g., Ujvary and Hanus , Cannabinoid Res, 2016, 1: 90-101). This possibility has importance for drug development, and for assumptions made of the properties of the parent molecule.

e. Need of the substance for other purposes (e.g. industrial)

No legitimate industrial or other use of CBD was identified although the review did indicate that some people were using CBD in skin and beauty products such as shampoos and skin creams.

f. Measures taken by countries to curb misuse

The review identifies six countries that control CBD. At the time of this peer review (20180517), Annex data from country surveys were not available to evaluate if other countries control it. Some countries, such as Canada, Australia and New Zealand, have relaxed control over CBD in recent years in part, to make it more accessible for medical use or research.

g. Impact if this substance is scheduled

Cannabidiol, when as an extract of cannabis, is already included in the Single Convention on Narcotic Drugs, 1961.

2. Are there absent data that would be determinative for scheduling?

It would be helpful to have additional information and detail regarding the ease of synthesis and resultant yields there are from laboratory conversion of CBD to THC to determine how practical this process is.

3. Other comments or opinions

The review indicates that "Some studies have shown that CBD may reduce or antagonize some of the effects of THC." This is a provocative observation, and it would be helpful to better understand the conditions under which this relationship

occurs to contrast with those conditions in studies that report that CBD can augment the abuse-related effects of THC (e.g., see McMahon LR., Drug and Alcohol Dependence, 2016, 165: 87-93).