World Health Organization
Expert Committee on Drug Dependence (ECDD)
ecddsecretariat@who.int

cc: Andrew Lee Ball, balla@who.int
Gilles Bernard Forte, forteg@who.int

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Contribution to Item 2 of the draft agenda: Preparations for consideration by the Commission of the proposed scheduling recommendations by the World Health Organization on cannabis and cannabis-related substances

Questions for the information meeting on 24 June 2019

1. Keeping cannabis in Schedule I of the 1961 Single Convention

The Committee found that cannabis is not associated with the same level of risk to health of most of the other drugs in Schedule I of the Single Convention on Narcotic Drugs as amended by the 1972 Protocol (the "Single Convention"), but then argued that because of *"the high rates of public health problems arising from cannabis use and the global extent of such problems",* cannabis should nevertheless remain in Schedule I. The review does mention *"a number of adverse effects associated with long term cannabis use"* and that cannabis *"can cause physical dependence in people who use the drug daily or near daily"*, but it is hard to see how the recommendation to keep cannabis in Schedule I can be reconciled with the ECDD's view that it is not associated with the same level of risk of most other drugs placed in Schedule I.

'High rates' or the 'global extent' of cannabis-related health problems are not a criterion for the similarity principle under the Single Convention – the basic threshold test for recommending whether cannabis should be placed in Schedule I (e.g., on a par with morphine and cocaine) or II (e.g., on a par with codeine). The similarity test requires evaluating whether cannabis is *"liable to similar abuse and productive of similar ill effects"* as drugs in Schedule I or Schedule II. As the Critical Review report on Cannabis and Cannabis Resin says: *"In terms of harm, most harm is caused by frequent or heavy use, especially heavy use over time [..]. Thus, prevalence of use* per se *is not a good indicator of public health harm"* (Section 5: Epidemiology, p. 40).

Questions:

1 (a) The ECDD seems to contradict itself regarding the issue of prevalence as a criterion for keeping cannabis in Schedule I and seems to have failed to apply the required similarity test. On the basis of which scientific data in the critical review documents does the ECDD conclude that the

abuse potential and ill effects of cannabis are more similar to drugs in Schedule I (with morphine and cocaine representing the basic standard for comparison), than to drugs in Schedule II (with codeine representing the basic standard)?[1] Or in fact that the similarity with either of those provides enough reason to recommend international control at all?

1 (b) The Single Convention itself[2] and the latest 'Guidance on the WHO review of psychoactive substances for international control'[3] both clearly establish that the required similarity test is the first test the ECDD has to perform to arrive at its recommendations, including in the case of proposed changes in the scheduling of substances already placed under international control.[4] On what basis was the decision made to add the prevalence criterion and how does the ECDD justify this apparent deviation from the clearly established rules of procedure in the Single Convention and the WHO Guidance?

2. Effects of the THC-CBD ratio in cannabis

The ECDD concludes that there is not "one cannabis", and that the actual content of the main psychoactive cannabinoid Δ9-THC (delta-9-tetrahydrocannabinol) can vary from very low (under 0.9% for the approved industrial varieties in the EU) to up to 28% (strength based on content of the flowering tops). Moreover, also the variety in cannabinoid profiles and the divergent presence of uptake enhancers causes a diversity of properties of the many cannabis varieties. The question is whether this makes a difference for the scheduling of cannabis and cannabis resin.

They may be agonists, partial antagonists, antagonists or pharmacologically inactive cannabinoids. Moreover, the non-psychoactive constituents may influence the uptake of the psychoactive and other constituents (e.g. terpenes) or may partially counteract the psychoactivity as a partial antagonist (e.g. (+)-cannabidiol (CBD) or cannabinol; the latter being a decomposition product). Both genotype and phenotype can make a difference for the actual composition of a cannabis batch.

1. The Technical Committee of the Plenipotentiary Conference stated that the substances which it listed for Schedule I were those "*Having addiction-producing or addiction-sustaining properties greater than those of codeine and more or less comparable to those of morphine; [or] Having a liability to abuse comparable to that of cannabis, cannabis resin or cocaine"*. The Commentary further explains that: *"The WHO has very wide discretion in selecting the Schedule. [..] It will be guided in this choice by the interest of public health in each case, as it appears not only from the degree of danger which the substance in question presents but also from the need to make useful medicines as easily available as may be compatible with the requirements of their control. Substances which are comparatively less dangerous and widely used in medical practice may therefore often be proposed for inclusion in Schedule II."* See: United Nations, *Commentary on the Single Convention on Narcotic Drugs, 1961*, New York: 1973, p. 86, par. 4; and p. 90, para. 16.

2. Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol, Article 3, "*Changes in the scope of control"*, paragraph 3(iii): *"If the World Health Organization finds that the substance is liable to similar abuse and productive of similar ill effects as the drugs in Schedule I or Schedule II or is convertible into a drug, it shall communicate that finding to the Commission which may, in accordance with the recommendation of the World Health Organization, decide that the substance shall be added to Schedule I or Schedule II."*

3. Guidance on the WHO review of psychoactive substances for international control, World Health Organization 2010, "*Step 1: 1961 Convention"*, paragraph 48: *"The Expert Committee, when deciding whether to recommend international control, or a change in international control, after completion of its discussions, first decides, with regard to the 1961 Convention, whether the substance in accordance with Article 3, paragraph 3 (iii) of that Convention: (1) is liable to similar abuse and productive of similar ill-effects as the substances in Schedule I or Schedule II; or (2) is convertible into a substance already in Schedule I or Schedule II."*

4. Ibid., "*Assessment for scheduling by the Expert Committee"*, paragraph 43: *"Proposals for the change in control of a substance should be subjected to the same assessment that is given to substances proposed for initial scheduling; the same criteria as mentioned below in paragraphs 46 to 59 should be used in making the assessment."*

These differences can have consequences for the psychopharmacological and other pharmacological activity of the plant.

Cannabinoids may affect the pharmacology of cannabis via two basic mechanisms: (1) the pure constituent may have pharmacological effects and/or (2) the constituent may interact with Δ9-THC and alter its effects (e.g., "entourage" effect). While the evidence base for the "entourage" hypothesis in general may still be weak, there is supporting evidence of pharmacokinetic interaction between CBD and Δ9-THC, in which CBD counteracts the level of psychoactivity of THC, and in particular the antipsychotic potential of cannabidiol.[5]

The Committee recommends for solid reasons not to schedule CBD, because it does not have psychoactive properties and has no potential for abuse and no potential to produce dependence. In order to resolve confusion in the past with regard to CBD, the Committee proposes to delete the ill-defined category of "Extracts and Tinctures" of cannabis from Schedule I of the Single Convention, which some states interpreted to include CBD oil, and to add a footnote clarifying that preparations containing predominantly cannabidiol and not more than 0.2 percent of Δ9-THC are not under international control.

The ECDD recommendations regarding THC and CBD recognize the difference of those cannabinoids in the pharmacology of cannabis, but fail to consider the ratio of both cannabinoids, other than the rather arbitrary 0.2 percent threshold of Δ9-THC in cannabidiol extracts, for which no scientific explanation is provided.

Questions:

2 (a) How did the Committee arrive at the threshold of 0.2 percent? Could this create conflicts with state practices that currently already apply higher THC thresholds in their domestic legislation, for example by defining "cannabis" with a threshold of 0.9 or 1 percent THC and exempting substances with a lower THC content from domestic control measures? In order to avoid such problems and further confusion, would it not be better to leave the definition of a precise threshold to the discretion of the Parties?

2 (b) Does the WHO agree that the ill effects and risks to health of cannabis depend on the ratio between the cannabinoids it contains, in particular THC and CBD, and that the level of the antagonist CBD in cannabis very much defines the psychoactivity of the substance. Should a scheduling recommendation based on the level of ill effects, the potential for abuse and the potential to produce dependence, not take this ratio into account? Has the ECDD for example considered the option that cannabis, resin and preparations containing a certain minimum percent of CBD could be excluded from international control, or could be added to Schedule III of the Single Convention,

5. Schubart C.D, Sommer I.E., van Gastel W.A., Goetgebuer R.L,. Kahn R.S., Boks M.P. (2011) Cannabis with high cannabidiol content is associated with fewer psychotic experiences. Schizophr Res. 2011 Aug;130(1-3):216-21. doi: 10.1016/j.schres.2011.04.017; Curran HV, Freeman TP, Mokrysz C, et al. (2016) Keep off the grass? Cannabis, cognition and addiction. Nat Rev Neurosci 17: 293–306; and Wall, M. B., Pope, R., Freeman, T. P., Kowalczyk, O. S., Demetriou, L., Mokrysz, C., … Curran, H. V. (2019). Dissociable effects of cannabis with and without cannabidiol on the human brain's resting-state functional connectivity. *Journal of Psychopharmacology*. https://doi.org/10.1177/0269881119841568

taking into account the nature of the admixtures and their degree of effectiveness in counteracting the dangerous properties of the drug?[6]

3. Adding dronabinol/Δ9-THC to Schedule I of the Single Convention

The ECDD applied the similarity principle to dronabinol/THC to recommend to move Δ9-THC (delta-9-tetrahydrocannabinol) to Schedule I of the Single Convention: *"As Δ9-THC is liable to similar abuse as cannabis and has similar ill-effects, it meets the criteria for inclusion in Schedule I of the 1961 Single Convention on Narcotic Drugs".*

This recommendation seems to be at odds with previous recommendations the ECDD has made on dronabinol/THC. On the basis of previous critical reviews of dronabinol, the ECDD recommended to reschedule it initially from the 1971 Convention's Schedule I to the less stringent Schedule II, which was adopted by vote in 1991. Ten years later, the Committee concluded that *"the very low rate of actual abuse of delta-9 THC suggest that the risk to public health may actually be less than required for substances to be included in Schedule II"*,[7] and recommended to reschedule it further down to the least strict Schedule IV of the 1971 Convention, a recommendation that was never passed on the CND for consideration. Subsequently, in 2006 the Committee recommended instead to reschedule it to Schedule III, a recommendation that was finally voted down by the CND in 2014.

In other words, all previous reviews of dronabinol led the ECDD to recommend a transfer to a less strict schedule, whereas now the recommendation to add it to Schedule I of the Single Convention means placing it under stricter control compared to its current placement (in Schedule II of the 1971 Convention). The recommendation on the part of the ECDD is not based on any new insights about greater harmfulness, but purely on the basis of the similarity principle compared with cannabis itself. There is a certain circularity in that argumentation, as the similarity test has not been applied to cannabis itself compared to other drugs in Schedule I.

Moreover it seems to be at odds with the latest WHO Guidance which establishes that: "*Any proposal to move a substance from one convention to another should be made only if specific new control measures are necessary in order to decrease the extent or likelihood of abuse or the use of the substance in illicit drug manufacturing, and will not unduly limit availability for legitimate medical and scientific purposes."*[8]

Questions:

6. See: United Nations, *Commentary on the Single Convention on Narcotic Drugs, 1961*, New York: 1973, p. 91, par. 7.

7. WHO Expert Committee on Drug Dependence, *Thirty-second report*, WHO technical report series no. 903, 2001, p. 19.

8. Guidance on the WHO review of psychoactive substances for international control, World Health Organization 2010, "*Assessment for scheduling by the Expert Committee"*, paragraph 45: *"A recommendation to delete a substance from one Convention with a simultaneous recommendation to add the same substance to another Convention may affect administration of the international scheme of regulation. Like all recommendations, consideration of such changes in control may be undertaken in light of new information to justify such a change. Any proposal to move a substance from one convention to another should be made only if specific new control measures are necessary in order to decrease the extent or likelihood of abuse or the use of the substance in illicit drug manufacturing, and will not unduly limit availability for legitimate medical and scientific purposes."*

3 (a) How does the ECDD explain the apparent discrepancy between the recommendation to move Δ9-THC (dronabinol) to Schedule I of the Single Convention and its previous recommendations to reschedule it to Schedule II (adopted in 1991), and subsequently to Schedule IV and then to Schedule III of the 1971 Convention?

3 (b) And in reference to the WHO Guidance, which "*specific new control measures"* did the Committee consider to be necessary for Δ9-THC and will transferring it from Schedule II of the 1971 Convention to the comparatively stricter Schedule I of the Single Convention *"not unduly limit availability for legitimate medical and scientific purposes"*?

4. The definition of exempted 'pharmaceutical preparations' in Schedule III

The ECDD recommends exempting under Schedule III of the Single Convention preparations *"compounded as pharmaceutical preparations with one or more other ingredients and in such a way that delta-9-tetrahydrocannabinol (dronabinol) cannot be recovered by readily available means or in a yield which would constitute a risk to public health"*.

No further clarification is provided about the criteria for easy recoverability, about the definition of 'compounded as pharmaceutical preparations', and how to distinguish those exemptions from the mixtures containing dronabinol/THC that would fall under Schedule I. It appears that on this point, the recommendations attempt to introduce a somewhat arbitrary distinction between products like Sativex and Marinol (which are specifically mentioned as examples) and other types of medicinal preparations based on cannabis extracts. The definition used for the exempted preparations, however, could also apply to many other mixed preparations with cannabis extracts for medical purposes. The vaguely-defined category of exempted preparations seems intended to provide a limited number of very specific products patented by pharmaceutical companies preferential treatment over a wide array of more natural cannabis extracts with similar medicinal properties.

Question:

4 Can the ECDD provide further clarification about the definition of 'compounded as pharmaceutical preparations', and confirm that is not limited to specific preparations like Sativex and Marinol but that Parties can apply that definition as well to mixtures of natural cannabis extracts with similar medicinal properties?