

WHO responses to CND on the 41st ECDD Recommendations

4th CND Intersessional Meeting, 24 June 2019, Vienna

5.0 General Questions

Cannabis has never been subject to a formal review by the WHO Expert Committee on Drug Dependence (ECDD) since its original placement within the International Drug Control Conventions. However, CND Resolution 52/5 requested WHO to provide an updated report on cannabis (subject to the availability of extrabudgetary resources). CND Resolution 50/2 also requested WHO, in consultation with INCB, as appropriate, to undertake a review of dronabinol and its stereoisomers when additional information became available. In addition, a number of countries have asked WHO to collect and analyse scientific evidence on harms and therapeutic use, due to the fact that some countries are currently exploring the feasibility of regulated access to cannabis and cannabis preparations for medical use.

In recent years, more robust scientific research has been conducted into the harms and therapeutic applications of cannabis and cannabis preparations. Importantly, since the adoption of the Single Convention on Narcotic Drugs, scientific research has clearly identified delta-9-THC to be the main psychoactive compound of cannabis. In the last few years, the WHO ECDD considered the amount of new evidence to be sufficient to carry out a formal review, to ensure a coherent and relevant level of international control that adequately considers current information about the harms and therapeutic uses of cannabis. This provided the basis for the ECDD review of cannabis.

The ECDD's recommendations seek to prevent the harms caused by the use of cannabis and cannabis preparations and ensure that they are available when and where they are needed for medical and scientific purposes.

In the context of the historical precedence of cannabis' original placement within the Conventions, of the development of new illicit cannabis preparations, and the new cannabis-related medicines entering into the market, the review of cannabis and cannabis-related substances was complex.

Because of the complexity of these reviews, WHO recognises the importance of communicating the rationale for the ECDD recommendations in a language that is well understood by experts, policymakers and other interested parties in countries. WHO will continue to engage in dialogue with these groups, within forums such as the CND intersessional as well as through bilateral meetings if requested.

WHO will also continue to work in close collaboration with Member States and other UN agencies such as UNODC and INCB to address the questions, concerns, and comments expressed by countries with regards to the scope of WHO's recommendations. For instance, WHO has received several questions regarding the production of cannabis, its industrial uses as hemp, and its use in food products. While these are important matters for Member States and the International community to consider, these issues are not within the mandate of the ECDD. WHO is prepared to address these issues in other forums involving other relevant UN agencies and interested parties.

WHO acknowledges the challenges faced by countries in enforcing balanced control policies that protect people from the harm arising from misuse of cannabis and ensure access to cannabis-based preparations for medical use for people who need them. WHO is aware of the public-health and social challenges caused by the misuse of cannabis, as has been highlighted by INCB in its 2018 report. WHO is committed to work closely with Member States and other UN agencies such as UNODC and INCB to ensure a smooth and efficient implementation of the recommendations, provided they are endorsed by CND.

5.1 Recommendation of Cannabis and Cannabis Resin

The decision of the Committee was to recommend that cannabis and cannabis resin, which are currently included in Schedule I and Schedule IV of the 1961 Convention, be controlled only under Schedule I.

Under the 1961 Convention, decisions as to scheduling, particularly for Schedules I and II, are based on similarity in liability to abuse and to produce ill-effects (convertibility is also a criterion but is not relevant for cannabis). The Committee had to take into account that cannabis also refers to preparations of cannabis and not just to the plant.

Substances in Schedule I, but not in Schedule IV, include the two other plants included in the 1961 Convention, coca leaf and opium, as well as the drugs cocaine, morphine, methadone and many other opioids.

The drugs in Schedule II are those considered to be weak opioids such as codeine and its derivatives. There are only ten such substances included in Schedule II. The Committee considered the evidence on liability to abuse and to produce ill-effects, and decided that cannabis and cannabis resin (understood to also include preparations of cannabis) were more similar to drugs in Schedule I than to the weak opioids such as codeine in Schedule II. That evidence is outlined in the Committee's report and more detail can be found in the critical review. However, some of the main points were as follows:

- In controlled laboratory studies, cannabis produces effects on mental state and behaviour typical of abused drugs.
- Dependence on cannabis is recognised and it includes the development of withdrawal symptoms on cessation of regular use. Approximately 1 in 10 cannabis users develop a cannabis use disorder.

- Cannabis has adverse effects that include impairment of cognitive function, impairment of driving, increased risk of psychosis, but it is not lethal and does not increase the lethality of other drugs.
- For some cannabis preparations with high THC content, the risks will be elevated above those due to cannabis in plant form.

Based on this evidence base, the Committee considered that the abuse and ill effects associated with cannabis and cannabis preparations exceeded those of codeine (and similar drugs) and were more similar to drugs in Schedule I.

With respect to Schedule IV, it should be recognised that only a small subset of the drugs in Schedule I are also included in Schedule IV. Apart from cannabis and cannabis resin, they comprise a subset of opioids that have been considered at various times to be particularly liable to abuse and to produce ill-effects, and to have no substantial therapeutic advantages. The drug most recently included in Schedule IV is carfentanil, an extremely potent and dangerous opioid that is not used in human medicine. As noted, neither opium nor coca leaf are included in Schedule IV. The Committee considered that neither the liability to abuse nor the liability to produce ill-effects of cannabis were commensurate with the other substances, such as carfentanil, in Schedule IV.

The Committee also acknowledged that in 1961, when the Convention was established and cannabis was included in Schedule IV, cannabis and cannabis preparations were not recognised to have any therapeutic use or therapeutic potential. There is now evidence that cannabis preparations have therapeutic advantages not possessed by other substances. This is being recognised by national regulatory authorities in a number of countries; for example, Sativex (containing both THC and CBD) has been approved for medical use in more than 30 countries. Based on both the level of liability to abuse and to produce ill effects of cannabis and preparations of cannabis, and the recognised therapeutic value of cannabis preparations, while acknowledging the characteristics of substances currently included in Schedule IV, the Committee considered that cannabis should not be included in Schedule IV.

With regard to the issue of impact on research, the Committee made an observation about the effect of scheduling that has been reported from some countries, but this was not critical to the decision to recommend deletion from Schedule IV. That impact will vary from country to country, depending on how Schedule IV is implemented.

With regard to the question “How does the committee reconcile its recommendation to maintain cannabis under Schedule I with the fact that the committee did not consider that cannabis is associated with the same level of risk to health of most of the other drugs that have been placed in Schedule I?”, it is important to consider the full sentence which is as follows: “While the Committee did not consider that cannabis is associated with the same level of risk to health, as that posed by most of the other drugs placed in Schedule I, it noted the high rates of public health problems arising from cannabis use and the global extent of such problems.” The problems referred to are detailed in the report, but included the high rate of cannabis disorders and the impact on driving.

With regard to the inclusion of cannabis preparations in Schedule III, the Committee has done so for cannabis-based pharmaceutical preparations with delta-9-THC (dronabinol) as the main compound.

It is important to note that the international control measures in place for a drug included in Schedules I and IV are the same as those for a drug in Schedule I. Therefore, there would be no weakening of the international control of cannabis if it was included only in Schedule I. For Schedule IV drugs, countries are encouraged to consider additional control measures, but such measures are not mandated by the 1961 Convention.

It is important to note that the levels of international control as recommended by WHO ECDD should be considered as a minimum requirement, and it is at the

discretion of Member States to implement more stringent levels of control depending on the specific country context.

5.2 Recommendation on delta-9-tetrahydrocannabinol (dronabinol)

The following is an extract from the report of the 41st ECDD meeting which addresses several issues raised in regard to dronabinol:

Dronabinol ((-)-trans- Δ^9 -THC), the active stereoisomer of Δ^9 -THC, was originally understood to refer only to this substance in its medicinal form. It is currently included under Schedule II of the 1971 Convention, but there have been several recommendations to change its status. Earlier recommendations to the CND were based on the understanding that Δ^9 -THC as a pure substance existed only in this medicinal form. However, particularly in the past 10 years, there has been increasing use of illicit substances prepared from the cannabis plant. These substances contain Δ^9 -THC with a range of purities, and particularly its active stereoisomer (-)-trans- Δ^9 -THC or dronabinol, up to 90% purity.

Thus, the difference between the recommendations some years ago and the recommendations currently under consideration, is the recognition that relatively pure forms of dronabinol exist not just as medicines, but also as illicit substances.

It is also important to recognise that while it has been said in the past, and is still frequently stated, that dronabinol refers to the medicinal form of THC, or dronabinol is the synthetic form of THC, neither are correct. Dronabinol is the international non-proprietary name for (-)-trans- Δ^9 -THC, whether it is found naturally in the cannabis plant or as a medicine. The inappropriate use of the term 'dronabinol' as a reference only to the medicinal form of THC has caused considerable confusion.

The reasons for the recommendation on dronabinol are described in the report of the 41st ECDD. In particular, it should be noted that the criterion for recommending that dronabinol be included in Schedule I of the 1961 Convention was the criterion of similarity in liability to abuse and to produce ill effects to cannabis and preparations of cannabis. It is also the case for opium and coca leaf that the plant and the drug that is included in the plant (morphine and cocaine, respectively) are controlled within the same schedule and the same 1961 Convention.

After the Committee consulted with INCB, it noted that:

... placing Δ^9 -THC under the same Convention and in the same schedule as cannabis, Schedule I of the 1961 Single Convention on Narcotic Drugs, would greatly facilitate the implementation of the control measures of the Conventions in Member States.

While this was not a criterion for the recommendation, and did not directly influence the recommendation, the ECDD did acknowledge that there were advantages to Member States should this recommendation be adopted.

The “Guidance on the WHO review of psychoactive substances for international control” through its paragraph 45, mandates WHO ECDD to recommend the move of psychoactive substances from one Convention to another. For WHO and the ECDD, this Guidance endorsed in 2010 by the WHO Executive Board, superseded previous advice concerning the transfer of substances from one Convention to another.

The same paragraph 45, states that a “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”. In line with this paragraph, the Committee recommended that dronabinol be scheduled under the 1961 Convention in particular because of illicit preparations containing high levels of

THC, such as butane hash oil. The existence and use of such high potency and harmful products is a relatively new phenomenon.

5.3 Recommendation on Tetrahydrocannabinol (isomers of THC)

The isomers of THC included in Schedule I of the 1971 Convention and recommended to be included in Schedule I of the 1961 Convention, along with the isomer dronabinol ((-)-trans- Δ^9 -THC) comprise a varied group of substances, most of which do not occur naturally. For none of them is there convincing evidence that would satisfy the criteria for inclusion in Schedule I of the 1971 Convention, as they are currently scheduled, and for at least one there is no such evidence. However, as the group of substances that is currently scheduled under a single drug name (tetrahydrocannabinol), they can be considered similar to dronabinol, as some do have dronabinol-like properties based on the limited evidence available.

It is also the case that as isomers of dronabinol they are very difficult to differentiate from dronabinol, through usual chemical identification processes.

The Committee took advice from INCB and recognised that the control of dronabinol would be compromised if these isomers were separately scheduled from dronabinol.

5.4 Recommendation on Extracts and tinctures of cannabis

In its recommendation to remove 'Extracts and tinctures', the Committee was not seeking to decrease the level of control of any cannabis related substance or narrow the scope of control. Should the recommendation be adopted no such decrease in control will occur.

Under the 1961 Convention, "preparation" is a general term covering mixtures, solids, or liquids containing a substance in Schedule I or II, and they are generally, if not entirely, subject to the same measures of control as that substance. In the case of opium and coca leaf, products derived from those plant sources are subject to the same measures of control as preparations, and the same is true of cannabis.

In the case of cannabis, currently there are three main types of illicit products derived from the plant:

1. extracts (obtained by use of a solvent; for example, butane hash oil),
2. tinctures (obtained using alcohol as a solvent), and
3. products derived without the use of a solvent but by application of heat and pressure.

All three types of products are controlled as preparations of cannabis. However, under 'extracts and tinctures' only the first two types are controlled.

The Committee therefore concluded that by relying on control of preparations of cannabis there is greater certainty of control of products derived, without the use of a solvent but by application of heat and pressure. These products are indistinguishable from those derived as extracts or tinctures.

While the Committee also noted that there was some potential for extracts and tinctures to include non-psychoactive preparations that are used medically (such as those containing CBD), the principal reason for recommending that 'extracts and tinctures' be removed, was so that there is greater certainty regarding control of all illicit products derived from cannabis, as cannabis preparations will be controlled in the same way as cannabis (Article 2 of the 1961 Convention).

With regard to products that contain mostly THCA and little THC, these are currently controlled as preparations of cannabis and would continue to be controlled in that way, should the recommendation to remove 'extracts and tinctures' be adopted.

Should dronabinol be moved to the 1961 Convention, preparations containing THC will be controlled, whatever method is used to produce them. Similarly, if the isomers of THC are moved to the 1961 Convention, preparations containing any of those isomers will be controlled, whatever method is used to produce them.

5.5 Recommendation on cannabidiol preparations

Cannabidiol (CBD) is a substance that can be synthesised or obtained from the cannabis plant. When obtained from the plant, under current regulations, it is controlled both as a preparation of cannabis (Schedules 1 & IV) and as an extract or tincture (Schedule I).

Cannabidiol shows no potential for abuse or dependence and any ill-effects are minimal. It is not similar to any other substance controlled under the 1961 Convention. Cannabidiol does have effects on the brain, but like many other substances with such effects, it is not considered psychoactive as it has no significant effects on mental state. Based on this evidence, and its value as a medicine, the Committee considered that cannabidiol should not be controlled under the 1961 Convention.

The Committee considered the option of including preparations of cannabidiol in Schedule III of the 1961 Convention. However, that Schedule is for drugs that are controlled and that satisfy the criteria for control. Cannabidiol does not satisfy those criteria. Inclusion in Schedule III lessens the degree of international control but a number of controls are still required. Inclusion of cannabidiol preparations in Schedule III would mean that controls would be required for preparations of a drug that did not satisfy the criteria for inclusion in the schedules of the 1961 Convention.

The option of a footnote was adopted after recognition of the precedents of exclusion of dextromethorphan and dextrorphan from control by this means.

When produced from the plant (as is the case with the cannabidiol medicine approved in the US and submitted for approval in other countries), cannabidiol preparations will contain trace amounts of THC as well as other cannabinoids and non-cannabinoid plant substances.

The Committee considered that most of the preparation should be CBD, and no more than 0.2% THC (by weight). The word predominantly was used to describe the proportion of CBD and this was intended to mean that almost all of the content was CBD. The Committee considered that the percentage of CBD to be used in practice could be left to individual Member States in consultation with INCB.

The value of 0.2% for THC was specified as WHO had requests from Member States to indicate what maximum percentage was considered appropriate and to ensure that the currently registered CBD medication was exempted from control. That medication has a THC content not greater than 0.15% by weight as a proportion of the total weight of plant material.

The Committee also acknowledged that chemical analysis of Δ^9 -THC to an accuracy of 0.15% may be difficult for some Member States and hence ECDD adopted a limit of 0.2%. On the basis of the Committee's recommendation, even for a maximum adult dose of CBD, the level of THC (max. 0.2%) will be below the level that would produce significant effects.

Cannabidiol preparations for medical use include preparations with a pre-marketing authorisation and could also include magistral preparations executed in pharmacies, if authorised in countries.

The Committee was aware that CBD products, such as foods, are being sold in many countries. While CBD does not satisfy the criteria for control under the 1961 or 1971 Conventions, Member States can regulate its availability using their own national legislation.

Both THC and CBD are present in the plant in acid form (THCA and CBDA). The acids of each are converted to THC and CBD, respectively, by heat and/or ultraviolet light. Thus, any product that contained predominantly CBD would not contain significant amount of THCA.

There are no implications for the control of cannabis plants or hemp plants arising from this recommendation.

With regard to other cannabinoids that may be devoid of psychoactive effects e.g. cannabidavarin (CBDV), the Committee considered that each should be considered separately. While there are such substances under investigation for potential therapeutic benefits, this research is in very early stages.

With regard to the conversion of CBD to THC mentioned (Japan), this method was described in a scientific paper over 50 years ago (Gaoni, Y. and R. Mechoulam, Hashish-VII. The isomerization of cannabidiol to tetrahydrocannabinols. Tetrahedron Vol. 22. 1966. 1481–1488) and has been the subject of a patent application.

The method is not simple and requires access to a number of chemicals, including certain acids and solvents. The yield is also uncertain, as are the by-products and their side-effects. This would be an expensive and potentially risky method of obtaining THC compared to use of cannabis and hence it is extremely unlikely that it would be implemented.

5.6 Recommendation on Pharmaceutical Preparations of Cannabis and delta-9-tetrahydrocannabinol (Dronabinol)

Preparations in Schedule III of drugs controlled in Schedule I or Schedule II of the 1961 Convention are exempted from some of the requirements for control of those drugs. However, they are still subject to a significant level of control.

Article 2 para 3 of the 1961 Single Convention states:

Preparations in Schedule III are subject to the same measures of control as preparations containing drugs in Schedule II, except that article 31, paragraphs 1 (b) and 3 to 15 and, as regards their acquisition and retail distribution, article 34, paragraph (b), need not apply, and that for the purpose of estimates (article 19) and statistics (article 20,) the information required shall be restricted to the quantities of drugs used in the manufacture of such preparations.

This makes clear that the exemption for Schedule III products is for some of the requirements only, and not an exemption from control.

The Committee considered the evidence regarding pharmaceutical preparations, including Sativex[®]. Based on conventional usage of the term, pharmaceutical preparations are those that are used for defined medical purposes and therefore that are in dosage forms appropriate for such medical use.

These pharmaceutical preparations encompass the ones requiring pre-market approval and the ones produced extemporaneously according to a prescription and to agreed good manufacturing practices. It was considered that individual Member States will have their own criteria for assessing whether a product is for medical use and as addressed in their national legislation.

The evidence from medical use of these preparations showed that they were not associated with abuse or dependence.

This recommendation is still relevant if the recommendation to move dronabinol (delta-9-THC) to the 1961 Convention is not supported, as the medications may contain dronabinol derived from the cannabis plant and therefore qualify as preparations of cannabis. As they would therefore be subject to control under the 1961 Convention, inclusion of the pharmaceutical preparations in Schedule III is still appropriate.

The pharmaceutical preparations recommended to be placed under Schedule III have dronabinol as the active ingredient and the recommended dosage will vary according to factors such as the conditions being treated and patient history.