Joint EIHA – FAAAT contribution to the 39th ECDD evaluation of Cannabidiol

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Abstract

Cannabidiol, specifically (-)-trans-Cannabidiol (CBD), can be isolated from plants of genus Cannabis, or produced synthetically. This chemical substance has a wide variety of uses, from maintaining, supporting and optimizing homeostasis to restoring, correcting and modifying it.

There is **no scientific justification or rationale to amalgamate CBD with substances under international control, even though** it may be extracted from the *Cannabis sativa L.* plant – if indeed done so (usually from industrial hemp varieties as registered by the OECD scheme), the substance can easily be chemically purified and isolated as a pure compound, practically free from other cannabinoids (in particular free from THC) and therefore free from any psychotropic or narcotic properties. Moreover, it is possible to produce naturally occurring CBD, namely (-)-trans-Cannabidiol, by chemical synthesis from small building blocks, a method that really has nothing to do with *Cannabis*[1]. The crude product (mostly a mixture of optical isomers) may be purified by known chromatographic methods, which results in nature-identical CBD.

This fact is acknowledged by the classification of CBD as an API (active pharmaceutical ingredient), and by the description of Cannabidiol in the substance's monograph C-052 in the German Drug Codex, DAC/ NRF, which does not differentiate between products of synthetic or natural origin: "The substance [(-)-trans-CBD] can also be produced synthetically"[2]. It also is the basis for the use of this pure substance as an ingredient for cosmetics, food supplements, and electronic cigarette liquids in lower concentrations.

Therefore the "CBD" substance under pre-review should be understood solely as pure Cannabidiol of whatever origin, i.e. CAS Number 13956-29-1, IUPAC name 2-[(1R,6R)-3-methyl-6-prop-1-en-2-yl-1-cyclohex-2-enyl]-5-pentylbenzene-1,3-diol.

There is no more scientific justification or rationale for scheduling CBD based on its assumed psychotropic properties: contrary to (-)-trans-Δ^9-Tetrahydrocannabinol (THC), which is also present in *Cannabis sativa L.*, CBD does not have any psychotropic effects and does not exert an euphoriant action. Furthermore, there is evidence from scientific literature that CBD moderates and reduces the psychotropic effects of THC. During its 38th meeting, the WHO's Expert Committee on Drug Dependence acknowledged that "cannabidiol [...] has little or no potential for abuse"[3].

United Nations Office on Drugs and Crime differentiates between drug-type versus fibre-type cannabis by a formula where sum of THC and CBN (Cannabinol) are divided by CBD. "If the peak area ratio of [THC+CBN] : [CBD] is ‹1, then the cannabis plant is considered to be a fibre-type. If the ratio is ›1, it is considered a drug-type"[4].

In conclusion, CBD is a substance that is beneficial to human health and public welfare. Subjecting it to appropriate legal sanitary regulation is justified, but it does not fit any of the requirements for inclusion in the international drug control treaty schedules.

1 Steup, C. (2015): Method for producing synthetic Cannabinoids. *European Patent* 2 314 580 B1
2 DAC/NRF 2016/2 C-052
3 White, J. (2016): Abuse dependence potential of Cannabis sativa and nabiximols, 38th ECDD (2016) Agenda item 5.1, page 20
4 UNODC (2009): Recommended methods for the identification and analysis of cannabis and cannabis products. page 20

Introduction

Cannabidiol (CBD) is one of the non-psychotropic and non-intoxicating active compounds in *Cannabis sativa L.*, a plant called "hemp" in vernacular English.

The last couple of years have seen a growing interest in CBD. Not only does Cannabidiol offer a plethora of beneficial health applications, it also has no relevant side effects, even when administered at high doses. It is increasingly used as an ingredient in cosmetics, in electronic cigarette liquids, and as a food supplement ingredient, thereby generating investment and creating employment in the fields of cultivation and processing of hemp and hemp-derived products. In 2016, 30,000 ha of industrial hemp were cultivated in the European countries, some 75,000 ha of hemp are cultivated in Canada and about 100,000 hectares in China.

We welcome WHO's comprehensive review of all cannabis-related substances but we strongly oppose classification of Cannabidiol as a psychotropic substance under international control. All scientific evidence shows that CBD has no intoxicating effects (Iffland and Grotenhermen, 2017 and references therein). Based on findings in scientific literature (Iffland and Grotenhermen, 2017 and references therein), scheduling CBD among the controlled substances does not hold up at all.

Researchers have also clearly shown that CBD is safe to use in a broad range of concentrations and indications, and has insignificant side effects compared to other similar nutraceutical products which are not included in the international treaties schedules.

Scheduling CBD would also have devastating implications on a worldwide hemp agriculture and industry reborn after almost a century of open or hidden oppression. Industrial segments, such as European automotive industry, would also greatly suffer if, a new psychotropic substance innate to hemp plant would have to be controlled.

I. Variety of Applications of Cannabidiol

1. Absence of abuse liability and dependence-producing effects

Contemporary evidence from the pharmacological sciences clearly shows that Cannabidiol is non-intoxicating and does not have any abuse potential or negative side effects on individual or public health and welfare. (Iffland and Grotenhermen, 2017).

Another comprehensive review on the safety and side effects of CBD has shown that even very high doses of the substance are safe and well tolerated, without significant side effects (Bergamaschi et al., 2011). In their meta-analysis of a total of 132 reviewed publications, it was found that CBD did not induce catalepsy, did not affect critical physiological parameters such as heart rate, blood pressure, body temperature, or gastrointestinal transit, nor did it alter psychomotor and cognitive functions.

The article by Russo (2017) explains that "CBD is frequently mischaracterized in lay, electronic, and scientific sources as 'non-psychoactive' or 'non-psychotropic' in comparison to (-)-trans-Δ^9-Tetrahydrocannabinol (THC), but these terms are inaccurate, given its prominent pharmacological benefits on anxiety, schizophrenia, addiction, and possibly even depression." Therefore, CBD should preferably and more accurately be labelled as 'non-intoxicating', seeing that it does not affect addiction parameters such as "reinforcement, craving, compulsive use etc.". The relevance of a drug abuse liability assessment can only be grounded on the existence of alterations of these factors produced or induced by the substance.

It has also been shown in various reports (such as the Czech Scientific Phytosanitary and Environmental Committee[5]) that "the toxicological studies on CBD products, and on comparable products, provided sufficient reassurance that the novel ingredient could be safe for the proposed uses."

The World Anti-Doping Agency (WADA) has recently exempted Cannabidiol from its list of Substances and Methods Prohibited "In-Competition". The note says: "Cannabidiol is no longer prohibited. Synthetic cannabidiol is not a cannabimimetic; however, cannabidiol extracted from cannabis plants may also contain varying concentrations of THC, which remains a prohibited substance."

In addition, The Novel Food catalogue published by the European Commission designates Cannabidiol as a "major **nonpsychotropic** constituent of the *Cannabis sativa* plant".[6]

Two renowned medicine control agencies testify to the absence of adverse or psychoactive properties of CBD: The European Medicines Agency (EMA), which declared that "Cannabidiol is present in the cannabis plant but it is not expected to have effects on mood, mental activity or behaviour."[7]; and the Australian Therapeutic Goods Administration (TGA), which claimed that "there is low risk of misuse or abuse as cannabidiol does not possess psychoactive properties."[8]

5 Scientific Phytosanitary and Environmental Committee, Czech Republic, Expert opinion 2/2017: Evaluation of "Cannabidiol CBDex" as novel food ingredient, March 27, 2017, page 17-18
6 http://ec.europa.eu/food/safety/novel_food/catalogue/search/public/index.cfm#
7 EMA/COMP/252372/2016, European Medicines Agency, Committee for Orphan Medicinal Products, 27 May 2016
8 TGA, Interim decisions on matters referred to an expert advisory committee: ACMS out-of-session, November 2014

2. Examples of health-related uses of CBD

The last INN listing from 2016[9] defines Cannabidiolum as a "cannabinoid receptor antagonist". This is further evidence of it actually reducing THC's effects, for example. Corroboration is provided by a letter from the Institute of Chemical Processes Fundamentals of the Czech Academy of Sciences: "Effects of ligands on CB1 receptors result in psychoactive effects evident with intake of d9-THC acting as CB1 receptor agonist. As per available sources CBD is a partial CB1 antagonist and his bonding on the receptor does not invoke psychoactive effect."

On another possible medical application, evidence is given in the 2016 EMA Committee for Orphan Medicinal Products report[10] titled "Public summary of opinion on orphan designation: Cannabidiol for the prevention of graft-versus-host disease", where Cannabidiol is described as acting "to reduce inflammation and other damaging immune effects and it is thereby expected to protect the patient's organs from injury."

3. Cosmetic applications of CBD

Amongst others, CBD can be used in several cosmetic applications. In the **unofficial EU database for information on cosmetic substances and ingredients**, CosIng, Cannabidiol is listed with four functional claims[11]:

- antioxidant,
- antiseborrhoeic,
- skin conditioning,
- skin protecting.

A letter by the Public Health Authority of the Slovak Republic[12] to EIHA states that "cannabidiol can be added to cosmetic products as a pure substance (**natural*** or synthetic) as well as a part of extracts from the plants or seeds of *Cannabis sativa*". Additionally, several CBD-containing products have already been certified and properly registered in INCI.[13].

4. Food applications of CBD

Cannabidiol is frequently used in food or food supplement products. The substance has even been listed in the European Union's Novel Food Catalogue[14], and the European Commission acknowledges that Cannabidiol is a cannabinoid and a major **non-psychotropic** constituent of the *Cannabis sativa* plant. At least one application for authorization of Cannabidiol use in food supplements is currently under evaluation.

5. Use of CBD in electronic cigarette liquids

There are no restrictions concerning the use of CBD in electronic cigarette liquids in many European countries as long as end-user products conform to the provisions of Directive 2001/95/EC on general product safety. These legal provisions acknowledge the fact that CBD helps fight nicotine addiction as a substitution product (Iffland and Grotenhermen, 2017 and references therein).

II. Recommendations

6. Policy perspectives for Cannabidiol

Of all the criteria considered in the Guidance on the WHO review of psychoactive substances for international control[15] (similarity with substances already in Schedules I or II of the 1961 Convention or Schedules I, II, III or IV of the 1971 Convention; convertibility into a substance scheduled under 1961 Convention; or the capacity of the substance to produce a "state of dependence" and "a central nervous system stimulation or depression, resulting in hallucinations, disturbances in motor function, in thinking, in behaviour or perception or mood"), none matches Cannabidiol.

Therefore, rather than applying the provisions of the international drug control conventions, obviously **irrelevant in this case**, national regulations related to Cannabidiol production and use should apply a comprehensive three-tier model[16] of doses and applications as outlined below:

- At high doses, over 200mg/average adult per day, the promising pharmaceutical applications of CBD require further clinical research. Policy makers should use the results of clinical research to allow evidence-based medicinal use of CBD.
- At physiological doses, between 20-200 mg/day, CBD should be regarded as an over the counter product, or a food supplement, similar to many substances, such as some vitamins and iron products, Valerian, glucosamine, chondroitin (sulphate), Ginkgo biloba, etc.
- Low CBD concentrations and doses below 20 mg/day should keep being allowed in food products without any restrictions.

9 WHO Drug Information, Vol. 30, No. 2, 2016, Proposed INN: List 115
10 ibid. EMA/COMP/252372/2016
11 http://ec.europa.eu/growth/tools-databases/cosing/index.cfm?fuseaction=search.details_v2&id=93486
12 Ref. OHVBPKV/9810/2016/Kr, November 30, 2016
* Emphasis added
13 EU CPNP: Cosmetic Products Notification Portal, https://webgate.ec.europa.eu/cpnp/public/tutorial.cfm
14 http://ec.europa.eu/food/safety/novel_food/catalogue/search/public/index.cfm
15 World Health Organization, 2010, ISBN 978 92 4 150055 5
16 http://eiha.org/media/2014/08/17-01-EIHA-CBD-position-paper.pdf

7. International classification of Cannabidiol and nomenclature issues

There is no reason to differentiate between Cannabidiol produced synthetically and by isolation from the cannabis plants. For example, DAC/NRF monograph C-052 mentions chromatographic purity between 98-102% and defines Δ^9-THC, Δ^8-THC and Cannabinol (CBN) as "specified impurities". Without prejudice of other legal requirements concerning the manufacture of the extracts of cannabis, considering "Cannabidiol" of natural origin as an "extract of cannabis" does not hold up to principles of the nomenclature of organic chemistry (IUPAC) system, Chemical Abstracts Service (CAS) as well as Harmonized System (HS Codes) of the World Trade Organization:

- Cannabis extract: CAS#: 89958-21-4, HS Code: 1302 19 – Vegetable saps and extracts
- Cannabidiol: CAS#: 13956-29-1, HS Code: 2907 29 – Phenols, phenol-alcohols

We can further substantiate our opinion based on the following citation: "A chemical substance (e.g., plant extract) used to produce a semisynthetic drug substance or a crude drug substance derived from a plant ... starting material is considered an intermediate"[17]. This statement makes clear that a plant extract used for isolating a pure chemical substance as an API is **NOT** the API itself, neither it is the medicinal product made from it. The plant extract is only an intermediate in the processing to yield to pure API.

Another important issue – although this point is of greater relevance for the Secretariat than for the experts – is the incorrectly translated wording of the biological effect of CBD in some of the WHO's official documents. Critically, the document entitled "WHO Drug Information, Vol. 30, No. 2, 2016, Proposed INN: List 115" mentions **cannabidiolum** as the International Nonproprietary Name for CBD on page 17, and states:

> *"EN: cannabinoid receptor antagonist*
> *FR: agoniste des récepteurs aux cannabinoïdes*
> *ES: agonista del receptor de cannabinoids"*

We hereby formally object to the attributes "agoniste" in French and "agonista" in Spanish, because CBD is an **ant**agonist of cannabinoid receptors. This should be rectified in the forthcoming List of Proposed INNs 115. We call on the Secretariat and the EMP department to attend to this confusing mistake with particular care.

III. Conclusions

CBD is a safe to use substance that is beneficial to human health and public welfare and has numerous applications in industry and nutrition, cosmetics as well as health and wellbeing products, besides its promising benefits in diverse indications such as reducing anxiety or helping people to quit smoking.

Applying the measures laid down in the international drug control treaties to Cannabidiol would severely restrict its availability for the non-problematic consumers of CBD and CBD-related products, as well as undermining safe access for many patients who already profit from CBD's manifold health-related and homeostasis-supporting effects. In addition to diminishing public welfare, employment in the blooming hemp industry would be actively destroyed, and the already existing and regulated market of non-therapeutical hemp-based products would shrink significantly, despite just having experienced a rebirth after almost a century of oppression.

Finally, Cannabidiol does not fit any of the requirements or criteria for inclusion in the international drug control treaty schedules, and it lacks the properties usually attributed to psychotropic substances or narcotic drugs.

Therefore we strongly urge the WHO to clearly recommend the exclusion of Cannabidiol from the scope of the international control measures, and reaffirm its unbelonging to the lists of internationally controlled substances.

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A plethora of additional empirical evidence may be obtained from EIHA.org, Dr. Bernhard Beitzke and Boris Baňas; moreover, digital copies of the cited material are available upon request.

17 FDA (2010): Guidance for Industry, Drug Substance Chemistry, Manufacturing, and Controls Information. Page 52

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