WHO Expert Committee on Drug Dependence Pre-Review:

Extracts and tinctures of cannabis

Expert Peer Review 2

1. Comments based on the review report

a. Evidence on dependence and abuse potential

Extracts of Cannabis include cannabis oils, aqueous extracts and cannabis tinctures derived from the cannabis plant. Cannabis undergoes an extraction process in order to separate the desired compounds such as cannabinoids or terpenes from the undesired products of the plant. The extracts come in various shades of color and consistency ranging from oily, butter, wax like, malleable to solids. The extracts have characteristic flavors and aroma and have various chemical or street names. A number of solvents have been used for cannabis extraction including hydrocarbon solvents, ethanol or aqueous products in order to have a subsequent final product. The potency of the final product is determined by the concentration of active cannabinoids primarily Δ⁹-tetrahydrocannabinol; Δ⁹-THC in the extract. Nabiximols is a unique cannabis extract with an approximate of 1:1 ratio of Δ⁹-THC and Cannabidiol (CBD) with other minor cannabinoids delivered as an oral mucosal spray for medicinal purposes.

Dependence potential:

There are no scientific studies that have evaluated dependence potential of pure cannabis extracts or nabiximols in animals. However, the psychoactive constituent Δ⁹-THC present in majority of the extracts has been separately examined and shown to have dependence potential as supported by animal and human studies. While there are no specific studies that have assessed the dependence potential of cannabis extracts in humans, it is likely that regular users of certain cannabis extracts with high concentrations of Δ⁹-THC would be more likely to become dependent. In the pre-review, cannabis oil extracts and concentrates contain the highest Δ⁹-THC concentrations while aqueous extracts containing the least concentrations. Hemp seed
oil extracted from the seeds of cannabis plants contain insignificant amounts of $\Delta^9$-THC. Few studies have demonstrated the lack $\Delta^9$-THC like psychoactive effects among hemp seed oil. In contrast, frequent butane hash oil use among cannabis users was associated with higher levels of physical dependence and perceived impaired control over cannabis use. There are no studies that have looked specifically for dependence potential for aqueous extracts.

The dependence potential of nabiximols has not been evaluated in humans. However, there is limited evidence of a withdrawal syndrome associated with nabiximols treatment. One study showed mild withdrawal symptoms including sleep disturbances, appetite changes, mood changes and vivid dreams following abrupt two week interruption of nabiximols treatment following long-term use.

**Abuse potential:**

There are no specific studies that have evaluated abuse potential of cannabis extract versus pure $\Delta^9$-THC in animals. There is evidence from animal studies indicating abuse potential of $\Delta^9$-THC when examined separately, which is a main constituent in many of the cannabis extracts. CBD also present in cannabis extract when examined separately, does not have abuse potential.

Cannabis extracts not only differ in concentrations of $\Delta^9$-THC and or CBD that they contain, but route of administration varies across cannabis extracts. In the pre-review, it was documented that the routes of administration varies across cannabis extracts in humans include sublingual, oral, inhalation (smoking or vaping), rectal and transdermal. Recent inhalational studies of cannabinoids in animal models have shown that exposure to cannabis smoke containing $\Delta^9$-THC produce comparable cannabinoid typical effects in rodents just as it does when $\Delta^9$-THC is administered by injection. Equally, suppression of locomotor activity, anti-nociception, hypothermia and catalepsy were observed in rats exposed to crude cannabis extracts or $\Delta^9$-THC using an e-cigarette device. In contrast, aerosolized $\Delta^9$-THC produced conditioned place preference in rats whereas intraperitoneal administration did not.

The abuse potential of nabiximols has not been specifically evaluated in animals. The two primary constituents of this botanical product have been tested ($\Delta^9$-THC and CBD) in drug discrimination and conditioned place preference models. In male Long–Evans rats trained to discriminate 3mg/kg $\Delta^9$-THC from vehicle, CBD appears not to exhibit THC discriminative stimulus effects. In contrast, CBD at 1:1 and 10:1 CBD: $\Delta^9$-THC ratios attenuated the conditioned aversive effects produced by 10mg/kg $\Delta^9$-THC in ICR mice. Whereas, in a select group of rats trained to self-administer i.v $\Delta^9$-THC, CBD did not affect $\Delta^9$-THC reinforcing effects.
In humans, there are no studies that have specifically evaluated abuse potential of cannabis extracts. The dosages of cannabis extract when consumed is rather determined by the user except for nabiximols. Vaping and smoking routes produce more rapid psychoactive effects. However, the abuse potential of high potency cannabis extracts via vaporizer has not been studied in humans. One double blind active comparator controlled study with an orally administered cannabis extract containing 2:1 ratio of $\Delta^9$-THC and CBD in drug naïve healthy volunteers found significant symptoms such as fatigue, drowsiness, dizziness and feeling high. Similarly, oral administration of $\Delta^9$-THC produces more sedation than smoking route.

In the preview, it appears that nabiximols has a dose related euphoric or subjective effects associated with cannabis use when evaluated in subjects with history of recreational cannabis use. There is no any abuse reported from Post market surveillance of Nabiximol.

b. **Risks to individual and society because of misuse**

There is scarce information regarding the individual risks associated with cannabis extracts, tinctures and aqueous extracts toxicity. The preview report described a comparative study which showed that both $\Delta^9$-THC and the cannabis extract equally increased the rate of resorptions in pregnant mice suggesting that compounds in cannabis extract do not modify the actions of $\Delta^9$-THC. There are a number of other individual risks such as the solvents used for extraction of the extracts can remain as residual solvents with potential health risks when ingested by the user. Similarly, there is a risk of contaminants such as pesticides being present in the final products in unregulated cannabis markets that can be easily transferred to the user via cannabis smoke. The thinning agents such as propylene glycol used in the vaping devices can produce toxic formaldehydes when heated. The combustion through smoking the cannabis extracts can also convert some of the compounds in the extracts to irritants or possible carcinogens.

Regarding cannabis tea, there is insignificant risk of toxicity with consumption of cannabis tea. Risk of toxicity regarding cannabis tinctures is also rare. A case report of mild cannabinoid poisoning in a child who consumed hemp seed oil with low levels of $\Delta^9$-THC has been reported, although toxicity risks with hemp seed oil in general appear to be rare.

It is likely that dose dependent intoxications in humans can be produced in cannabis extracts users with high $\Delta^9$-THC concentrations. However, there are no robust studies demonstrating this theoretical explanation. In the preview report, one study on butane
hash oil cannabis users showed greater restlessness, anxiety and memory impairment symptoms compared to high potency herbal cannabis users. Butane hash oil users were also more likely to have lifetime mental health problems and other illicit use of substances.

There is evidence of a significant risk of environmental fires and explosion due to solvent based manufacturing process in cannabis extract. There has been increasing cases of burn injuries related to production of butane hash oil or use of hydrocarbon solvents in the United States resulting in serious adverse events. In one study, of the twenty nine butane hash oil burn cases hospitalized, nineteen patients required skin grafting, eight wound care only, one surgical fracture repair and one surgical debridement. In another study, three fatalities and longer stay hospitalizations were reported. Compared to herbal cannabis use, one study did not demonstrate whether butane hash oil use was associated with more accidents or medical problems than use of flower (herbal) cannabis.

In the preview report, Nabiximols could transiently cause tachycardia, orthostatic hypotension but no cardiac conduction abnormalities reported. It appears that there was no indication of carcinogenic or mutagenic potential demonstrated in in vivo studies done in mice and rats. No evidence of fertility problems with supra-therapeutic doses of up to 12.5mg/kg/day of Δ⁹-THC and CBD. There is some risk of fetal toxicity in rabbits at higher dosage including low fetal weights and delayed ossification of the fetal skeleton. Low fetal weights and impaired righting reflex has been shown in rats offspring’s at doses of 4mg/kg/day. Evidence shows that oral administration of 1:1 mixture of Δ⁹-THC BDS and CBD BDS resulted into high concentration of the mixture in breast milk of lactating rats.

A number of adverse reactions following nabiximol use has been shown. They include dizziness, fatigue, distorted taste, dry mouth, nausea, mouth ulceration and burning sensation in mouth and tongue which can be mild and self-limiting. Neuropsychiatric side effects such as disorientation, depression, euphoria, and dissociation have also been reported. Transient psychotic reactions have been reported in some otherwise healthy individuals at supra-therapeutic dosage (e.g. 18 sprays twice a day).

There are no placebo controlled studies on nabiximol use on driving performance using driving simulators that has been evaluated. Preliminary evidence cited in the preview report showed no effect on driving related ability compared to baseline performance after 4-6 weeks of daily nabiximol use among patients with multiple sclerosis. There are no reported cases of driving under influence of nabiximol.
c. Magnitude of the problem in countries (misuse, illicit production, smuggling etc.)

Few studies have been documented related to cannabis extracts and tincture misuse. A global online survey from several countries reported, 3% of participants and 7% of the past year cannabis users (N=181,870 participants, 46% were cannabis users) using butane hash oil. The motives for use being recreational or medical use or in majority of respondents both recreational and medical reasons were cited. Two other surveys conducted in the US showed vaporization of cannabis oil and wax was found in 15.5% and 10.2% among lifetime cannabis users (n=1,123) and 22.9% and 14.8% among those with lifetime e-cigarettes. An additional study in the US found that among past year cannabis users, 44% (n=121) had used butane hash oil in the past year and that frequent butane use was associated with higher levels of physical dependence. There are no reports of misuse of nabiximols.

There seems to be no reports on global seizures or illicit production of tinctures or explicit cannabis extracts in the preview report.

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

Nabiximols has approved indications for treatment of spasticity and neuropathic pain due to multiple sclerosis (MS) and or chronic cancer pain in a number of countries. Cannabis extracts and tinctures are either undergoing trials or some being used under medical cannabis legislation to treat similar or other medical conditions.

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

Not known

f. Measures taken by countries to curb misuse

Possession and or manufacturing of cannabis extracts and tinctures remain illegal in most parts of the world. It is likely that in some states or countries where non-medical use of cannabis is legal, regulations on packaging or labelling or some form of ban on manufacturing of cannabis extracts e.g. of cannabis concentrates or butane oils is possible.(Refer to WHO questionnaire)

g. Impact if this substance is scheduled

Extracts and tinctures of cannabis are currently under Schedule I of the 1961 Convention.

2. Are there absent data that would be determinative for scheduling? Not applicable
3. Other comments or opinions

Globally, it appears that cannabis extracts and tinctures have a minimal role for recreational use compared to cannabis herbs and resin. There is a significant therapeutic role in some of the cannabis extracts and tinctures. In future, controlled studies based explicitly on cannabis extracts can help provide more insight into variations in abuse and dependence potential that may exist among different cannabis extracts given the variations in the concentrations of $\Delta^9$-THC and cannabinoids present in the various cannabis extracts.