Cannabidiol:

Submission to the Expert Advisory Committee on Drugs

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# INTRODUCTION

Cannabidiol (CBD) is one of 80 to 100 cannabinoids isolated from the cannabis plant (Victorian Law Reform Commission, 2015). It has little or no psychotropic activity and little affinity for the CB1 and CB2 receptors but acts as an antagonist of cannabinoid agonists (Pertwee, 2008).

Public interest in CBD products for medicinal purposes has increased with the emergence of CBD-only and CBD-based products. The majority of these emerging products are non-pharmaceutical grade but some pharmaceutical grade product is becoming available. Epidiolex is a pharmaceutical grade product undergoing clinical trials in the United States that is looking to be useful for treating rare forms of severe epilepsy, for example Dravet syndrome.

Current research indicates that CBD could have several therapeutic applications. Some of the effects that have been reported to date include anti-seizure, neuroprotective, anti-inflammatory, analgesic, anti-psychotic and anti-anxiety effects (Volkow, 2015; de Mello Schier, et al., 2012; Bergamaschi, Queiroz, Crippa, & Zuardi, 2011; Burstein, 2015; Hill, Williams, Whalley, & Stephens, 2012). However, more clinical trials are required to confirm the effectiveness of CBD for the various proposed indications and the lack of serious adverse events that have been reported so far (Cunha, et al., 1980; Bergamaschi, Queiroz, Crippa, & Zuardi, 2011; Burstein, 2015).

The question could be raised whether CBD should be a controlled drug, due to its lack of psychotropic effects and no reported serious adverse events. There is a view that it should only be a prescription medicine. More robust clinical trials are required to confirm the therapeutic uses and safety of CBD as a medicine. However, given the lack of psychotropic effects of CBD and its relative safety, there is argument for it to no longer be considered a controlled drug.

Additionally, it should be considered that most CBD extracts will have small amounts of Δ9-tetrahydrocannabinol (THC) and it can be difficult (and therefore expensive) to separate THC from CBD in extracts of cannabis. As THC is scheduled as a Class B1 controlled drug, any THC in a CBD medicine will cause it to fall under Misuse of Drugs Act 1975 (MoDA) regardless of the classification of CBD. Australia has recently addressed this when rescheduling CBD as a prescription medicine by allowing up to 2% of other cannabinoids found in cannabis (see Section 3.2 below).

The Committee is asked to review the classification of cannabidiol (CBD) and provide a recommendation on whether its classification should be retained or amended. The Committee is further asked to review the recent Australian scheduling change which rescheduled CBD with less than 2% of other cannabinoids as a prescription medicine only.

# 2.0 SUBSTANCE IDENTIFICATION

## 2.1 Chemical Names/ Trade Names

The IUPAC chemical name for cannabidiol is 2-[(1S,6R)-3-methyl-6-prop-1-en-2-ylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol (PubChem, Accessed March 2016). Although some variations of this name have been noted such as the replacement of the wording prop-1-en-2yl with 1-methylethenyl (ChemIDplus, Accessed March 2016; PubChem, Accessed March 2016). It has also been known as Resorcinol, 2-p-mentha-1,8-dien-3-yl-5-pentyl- (PubChem, Accessed March 2016). However, it is most commonly known as cannabidiol or CBD.

## 2.2 Origin and History

Cannabis is the common name used for the two main species of plants; *Cannabis sativa* and *Cannabis indica*. Cannabis is also the internationally agreed descriptor and the term used in the Single Convention on Narcotic Drugs, 1961. Cannabis has been used for thousands of years for many applications from clothing and rope to medicines and recreational drug use (Devinsky, et al., 2014).

Cannabidiol is one of the major components of *Cannabis sativa* along with THC. While both components are neuroactive, CBD is not psychoactive like THC, this means that it does not produce a “high” like THC (Devinsky, et al., 2014; Kramer, 2015). For this reason little research was done on CBD in the past when compared to THC as the psychoactive properties of THC meant it was assumed to be the active component of cannabis and therefore CBD was assumed to be inactive (Burstein, 2015; Zuardi, 2008).

## 2.3 Chemical Makeup

Cannabidiol (Figure 1) has the chemical formula C21H30O2 and CAS number 13956‑29‑1. It has two chiral centres at the 1 and 6 position of the cyclohexenyl structure (denoted by the two single hydrogen atoms in the structure), two alcohol functionalities and two isolated double bonds in addition to the aromatic benzene.



Figure 1 Chemical structure of cannabidiol (CBD)

## 2.4 Similarity to Other Known Substances

CBD is very similar in structure to its structural isomer THC (Figure 2). Looking at the 2D structure of these two shows that the difference in the structures is the cyclisation of the hydroxy at the 1 position of the benzene with the propenyl side chain of the cyclohexenyl structure (Figure 3). However, the conformation of these structures (how they sit in three dimensions) is very different. THC has an essentially planar structure due to the fused rings of the backbone cannabinol structure. However, CBD has the two rings at right angles to each other due to the freedom to rotate around the bond connecting the cyclohexene and benzenediol structures. This is thought to be the reason that CBD does not bind to or activate CB1 receptors in the body like THC does and thus explains why it is not psychoactive (Burstein, 2015). The conformational differences can be seen in Figure 4 below.

Figure Electron movements (shown by the blue arrows) required in the conversion of cannabidiol to tetrahydrocannabinol

Figure Chemical structure of Δ9‑tetrahydrocannabinol (THC)

Figure Cannabidiol (CBD) 3D conformation (top) and Δ9‑tetrahydrocannabinol (THC) 3D conformation (bottom). (PubChem, Accessed March 2016)


# 3.0 REGULATION/ CLASSIFICATION

## 3.1 Current Regulation/ Classification in New Zealand

## Cannabidiol is a Class B1 controlled drug under the isomer provision of MoDA Schedule 2 Part 1.

It has recently been questioned if CBD is controlled under MoDA, as has been believed for some time. The Ministry believes that CBD is an isomer of the controlled cannabinoid THC and that CBD is within the specific chemical designation of THC as described in the isomer provision.

CBD is also listed as a prescription medicine in the Medicines Regulations 1984 because it is a controlled drug that is used for a medicinal purpose. This means that it has not been reviewed by the Medicines Classification Committee prior to scheduling in the same way that other prescription medicines that aren’t controlled drugs have been.

Most CBD extracts will have small amounts of THC and it can be difficult (and therefore expensive) to separate THC from CBD in extracts of cannabis. Any THC in a CBD medicine will cause it to fall under MoDA irrespective of the classification of CBD, as THC is scheduled as a Class B1 controlled drug.

Sativex, which has a 1:1 ratio of CBD to THC is a Class B1 controlled drug and an approved prescription medicine under the Medicines Act 1981.

In the Misuse of Drugs (Industrial Hemp) Regulations 2006, THC content generally below 0.35% is allowed and no more than 0.5%. The purpose of the Industrial Hemp Regulations is to enable the cultivation and distribution of industrial hemp under a licensing regime that ensures that other forms of cannabis are not cultivated under the guise of industrial hemp. “Industrial hemp” is only defined by the level of THC in the hemp (CBD or other cannabinoids are not mentioned). The definition of hemp products does not specifically exclude products for therapeutic purposes, however it is considered that this legislation was not intended to be used for regulating medicinal uses of cannabis. Cannabis for medicinal purposes is regulated under MoDA.

## 3.2 International Classification and Experience in Other Jurisdictions

**Australia**

The Therapeutic Goods Administration (TGA) have recently down-scheduled CBD to a Prescription Only Medicine “in preparations for therapeutic use containing 2 per cent or less of other cannabinoids found in cannabis”. It is now listed in Schedule 4 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP), also known as The Poisons Standard. This change means that the process in Australia for prescribing CBD with less than 2% of other cannabinoids is the same as for any other prescription medicine with no additional approvals or processes required.

The following comments were made on its scheduling (Therapeutic Goods Administration, 2015):

* The condition that cannabidiol treats (the therapeutic use) requires diagnosis, management and monitoring under an appropriate medical practitioner.
* Cannabidiol has a safety profile which is consistent with a Schedule 4 listing.
* There is low risk of misuse or abuse as cannabidiol does not possess psychoactive properties.
* The schedule entry needs to acknowledge that there is no pure form of cannabidiol currently available. However, low levels of impurities found in some cannabidiol products are not clinically significant and the scheduling entry should reflect this by allowing cannabinoids, up to 2%.
* The entry allows for but does not specify any particular non-active cannabis impurity/ies to be within the up to 2%.
* The substances that comprise the up to 2% must be substances found in cannabis. They cannot be synthetic cannabinoids.
* The entry does not preclude the cannabidiol and/or any other cannabinoids being derived from natural sources or made artificially, consistent with the interpretation of the schedules.
* It is considered that it is the medical condition for which CBD may be used which requires treatment by a specialist… Scope of practice will ensure the appropriate prescribing of cannabidiol rather than scheduling.

**Internationally**

The classification of CBD internationally is inconsistent both between countries and within countries. For example, in the USA, cannabis has a Schedule 1 (controlled drug) classification federally and this includes CBD. However, Several US states have recently legalised the growing and selling of cannabis for recreational use. There are also a variety of state laws and regulations on the medical use of cannabis (and therefore CBD) in the USA.

## 3.3 UN Classification

Cannabidiol is not specifically scheduled by the Single Convention on Narcotic Drugs 1961. However, it can be captured under cannabis and cannabis resin which are Schedule 1 and Schedule 4 Narcotic Drugs. The Schedule 4 listing enables parties to the convention to adopt special measures of control as necessary according to the prevailing conditions in its country. There are special requirements relating to the cultivation of cannabis.

# 4.0 RISK OF HARM IN NEW ZEALAND

## 4.1 Specific Effects

Cannabinoid compounds including THC work as agonists of the G protein-coupled receptors CB1 and CB2. CB1 receptors are present in neurons in several brain regions at very high levels. These receptors mediate many of the psychoactive effects of cannabinoids. CB2 receptors have a more restricted distribution and are localised in a number of immune cells and in a few neurons (Mackie, 2008).

CBD has a low affinity for CB1 and CB2 receptors, however, it has been found to interact with these receptors at low concentrations as an antagonist of CB1/CB2 receptor agonists (Pertwee, 2008). The differences in affinities for CBD and THC for these receptors is thought to be due to the conformational differences between CBD and THC (as discussed in Section 2.4) the result being that CBD does not have a psychoactive effect while THC does (Burstein, 2015).

While more research is needed, early reviews suggest that CBD may be well tolerated in humans including at high doses and with chronic use (Bergamaschi, Queiroz, Crippa, & Zuardi, 2011; Hill, Williams, Whalley, & Stephens, 2012; Cunha, et al., 1980). One adverse event that has been noted during a clinical trial is somnolence (Cunha, et al., 1980).

## 4.2 Likelihood or Evidence of Abuse

CBD on its own is unlikely to have the potential for abuse as it does not produce a psychoactive effect like that of THC. This is also the view taken by the TGA as detailed in Section 3.2. However as noted in Section 4.6 it is readily converted to THC. No evidence has emerged yet of pure CBD being used as a THC precursor but this possibility needs to be noted.

## 4.3 Physical or Psychological Dependence

Physical or psychological dependence on CBD does not appear to have been tested to date. However, studies which have been conducted indicate that there is a lack of psychotropic effects and do not indicate any evidence of dependence associated with its use (Cunha, et al., 1980; Bergamaschi, Queiroz, Crippa, & Zuardi, 2011).

## 4.4 Potential to Cause Death

CBD is considered to be well tolerated in humans at high and chronic doses, however, more research and clinical trials is needed into this area. More research is also needed into the interactions with other drugs and medicines (Bergamaschi, Queiroz, Crippa, & Zuardi, 2011).

## 4.5 Therapeutic Value

While there is insufficient clinical data to determine the potential of CBD to treat specific conditions, some pre-clinical research has been done that demonstrates a range of effects that would be therapeutically valuable if confirmed with robust clinical data. These effects include anti-seizure, neuroprotective, anti-inflammatory, analgesic, anti-tumour, anti-psychotic and anti-anxiety (Volkow, 2015; de Mello Schier, et al., 2012; Bergamaschi, Queiroz, Crippa, & Zuardi, 2011; Burstein, 2015; Hill, Williams, Whalley, & Stephens, 2012). There are very few robust clinical trials that have been performed on the medical use of cannabis or CBD and most adverse events reporting currently comes from recreational use of cannabis. This is a cause for concern for some when considering the scheduling of medicinal cannabis (Victorian Law Reform Commission, 2015; Welty, Luebke, & Gidal, 2014; Mathern, Beninsig, & Nehlig, 2015).

## 4.6 Risks to Public Health

CBD can be readily converted to THC by acid catalysed cyclisation (Mechoulam & Hanus, 2002). In the past this has been shown by boiling CBD in 0.05% hydrochloric acid in ethanol to produce THC (Gaoni & Mechoulam, 1966). It is for this reason that the argument could be made for cannabidiol not to be excluded from the current isomer provision of MoDA for THC as the reference to isomers, esters, ethers and salts of substances is included in MoDA because they are easily converted to the parent substance (Bedford, 2015). However, as previously stated, there is currently no evidence of pure CBD being used as a THC precursor.

# 5.0 ANTICIPATED FUTURE TRENDS

Currently, research is being undertaken to explore the medicinal uses of cannabis and CBD. Once more clinical trial information has been collected and reliable conclusions can be drawn, CBD may become more widely accepted by healthcare practitioners. There is also increasing public demand for medicinal cannabis, although approval of medicinal CBD products with low THC may not be seen as going far enough.

# 6.0 OTHER RELEVANT INFORMATION

**Should CBD be a controlled drug?**

Cannabidiol has little evidence of the features that would require it to be a controlled drug. CBD does not produce psychotropic effects like THC. There have been no serious adverse events associated with CBD use reported and it has been shown to have potential therapeutic benefits. Removing the controlled drug status of CBD would enable research on this drug to be more freely done. This could result in confirmation of the therapeutic potential and a better understanding of the safety profile for CBD.

However, the ease of conversion of CBD into THC is a factor that must also be considered.

**Impact if CBD is not scheduled under MoDA**

CBD is currently already a prescription medicine and therefore has significant controls placed on its use and supply. There are no approved CBD-only medicines available. This means that CBD products would be treated as unapproved medicines applications until a suitable CBD medicine application could be approved.

Police have indicated that they have no records of any prosecutions for CBD possession or supply.

**THC levels**

It can be difficult to separate THC from CBD in extracts of cannabis and therefore most CBD extracts may have small amounts of THC. As THC is scheduled as a Class B1 controlled drug, any amount of THC in a CBD medicine will cause it to fall under MoDA. This means that if CBD should no longer be classed as a controlled drug, then there may need to be provisions made within MoDA to allow a certain amount of THC in prescription medicines below a certain threshold. Without this, it is possible that if approved CBD products become available they will still require ministerial consent (delegated to Ministry officials) before they can be prescribed.

As mentioned in Section 3.2, the TGA have recently allowed CBD to be used in prescription medicines with no more than 2% of cannabinoids found in cannabis While the reasons noted for the rescheduling of CBD include allowing up to 2% of non-active cannabis impurities, the amended legislation does not specify that the “other cannabinoids found in cannabis” are inactive. It may be that the assumption is that other cannabinoids would be inactive at this dose.

The concentration of THC in Sativex is 2.7%. If the other cannabinoids in a CBD preparation were principally THC then it could be possible to have a therapeutic effect at a 2% level.

It is possible that New Zealand could mirror the TGA and allow up to 2% of cannabinoids found in cannabis in CBD preparations. However, it could also be argued that a 2% limit is high and New Zealand should have a lower limit. With an allowance of THC there will be the potential for abuse, however this risk should be minimised by the prescription medicine classification of CBD. A limit of THC allowed in CBD products would be required if a pragmatic approach were to be taken to the medicinal use of CBD.

# 7.0 SUMMARY

Cannabidiol is a non-psychotropic component of cannabis. Current research indicates that CBD could have many potential therapeutic applications and the use of CBD is not associated with serious adverse events. More robust clinical trials are required to confirm the therapeutic uses and safety of CBD as a medicine. However, given the lack of psychotropic effects of CBD and its relative safety, there is argument for it to no longer be considered a controlled drug. The Ministry currently considers CBD a class B1 controlled drug under MoDA as an isomer of THC, however, the status needs to be reviewed to consider if CBD should be classified as a prescription medicine only.

Given that THC is present in most CBD extracts of cannabis an allowance for THC in CBD products also needs to be considered.

# 8.0 CLASSIFICATION OPTIONS

**Option 1: Status quo**

Option one would be to leave the current CBD classification as it is. Cannabidiol is currently classified as a Class B1 controlled drug under the isomer provision of MoDA as an isomer of the Class B1 controlled drug THC.

Under MoDA, the penalty for anyone caught in possession of a Class B controlled drug for personal use is a maximum of 3 months imprisonment and/or a $500 fine. Anyone convicted of any offence related to dealing of a Class B controlled drug (importing, manufacturing, selling, supplying or possessing with the intent to sell) faces up to 14 years imprisonment.

**Option 2: Scheduled as a prescription medicine only**

Option two would be to deschedule CBD from being captured under MoDA so that it is classified as a prescription medicine only.

Under the Medicines Act 1981, prescription medicines can only be accessed with a prescription given by an authorised prescriber, veterinarian or delegated prescriber. However, if THC was present in the preparation the MoDA penalty stated in Option 1 would apply.

**Option 3: Alignment to Australia**

Option three would be to deschedule CBD from being captured under MoDA so that it is classified as a prescription medicine only. In addition to this, a provision in MoDA would be recommended for allowing other cannabinoids found in cannabis up to 2% in CBD preparations.

# Under the Medicines Act 1981, prescription medicines can only be accessed with a prescription given by an authorised prescriber, veterinarian or delegated prescriber.

**Option 4: Scheduled as a prescription medicine with a provision for other cannabinoids found in cannabis**

Option three would be to deschedule CBD from being captured under MoDA so that it is classified as a prescription medicine only. In addition to this, a provision in MoDA would be recommended for allowing other cannabinoids found in cannabis in CBD preparations. The proposed limit of this provision would be specified by the EACD.

# Under the Medicines Act 1981, prescription medicines can only be accessed with a prescription given by an authorised prescriber, veterinarian or delegated prescriber.

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