

Medicinal Cannabis Industry Australia

Position Paper - Delta-8 Tetrahydrocannabinol (Delta-8 THC)

1.0 Purpose of this position paper

MCIA is focused on development of the medicinal cannabis sector and works within the legal framework established by Federal and State Governments

There has been some recent media attention in relation to medicinal cannabis Delta-8-Tetrahydrocannabinol products (manufactured from hemp CBD) and the appropriateness of these as imported products in Australia, as well as health and safety concerns.

This paper is designed to provide some background on Delta-8-Tetrahydrocannabinol products to assist members and others who may have questions around these products. This paper is not intended as any formal advice or position and should not be relied on as health or personal advice, and anyone handling these products or with specific questions should seek specific legal or other technical advice from appropriate experts.

1.1 Legal framework regarding imports

Cannabis products, including substances such as delta-8-THC, are regulated through a number of Australian Acts and Regulations. These include the *Narcotic Drugs Act 1967 (ND Act)*, the *Therapeutic Goods Act 1989 (TG Act)* and the *Customs (Prohibited Imports) Regulation 1956 (PI Regulations)*. Australia is also a party to the Convention on Psychotropic Substances of 1971 (**Convention**). Delta-8-THC is a schedule 1 drug under the Convention and thus, in Australia, must be manufactured, imported and exported in accordance with the Convention. As such, imports are subject to licence and permit issued by the Office of Drug Control.

The *Therapeutic Goods (Standard for Medicinal Cannabis) (TGO 93) Order 2017 (TGO 93)* provides the requirements for the identification of each active ingredient, including the quantity or proportion, where it falls within a stated range. Where an active ingredient falls outside the lower end of the range it is not required to be shown. Cannabinoids in excess of 2% or THC in excess of 1% of the preparation are taken to be active ingredients. TGO 93 does apply to a product containing delta-8-THC, with the requirements outlined representing the minimum quality standard for medicinal cannabis products.

For unapproved medicines accessed through the Special Access Scheme (**SAS**) or Authorised Prescriber (**AP**) pathways, manufacture under Good Manufacturing Practice (**GMP**) is assumed to be inherent given their approval by an overseas medicines regulator. Accordingly, SAS and AP pathways for imported products do not currently require GMP evidence to be supplied or held by a Sponsor for Medicinal Cannabis products, as compared to medicinal cannabis products manufactured in Australia which must be manufactured under TGA issued GMP Licence.

TGA have advised that updated guidance for sponsors regarding imports will be published by March 2022 as a result of consultations held in January 2021. This is expected to provide guidance around what evidence sponsors must hold to confirm that each batch of imported goods was manufactured in accordance with international codes of GMP equivalent to Australian TGA GMP.

It should be noted that TGA's ingredients list currently only includes a single listing for tetrahydrocannabinols i.e. ingredient ID19887 with a stated synonym of Delta-9-Tetrahydrocannabinol. There is currently no delineation between Delta-9-THC and Delta-8-THC, however, MCIA understands that TGA is investigating this to ensure labels are appropriate.

2.0 Delta-8 Tetrahydrocannabinol (Delta-8 THC)

- ❖ “THC” generally refers to delta-9 tetrahydrocannabinol (delta-9 THC); the dominant psychotropic compound naturally occurring in *Cannabis*.
- ❖ Delta-8 Tetrahydrocannabinol (delta-8 THC) is an isomer of delta-9 THC – having the same chemical formula but a different chemical structure.
- ❖ Delta-8 THC has been reported in trace amounts in *Cannabis*.
- ❖ Delta-8 THC can be and is produced by treating cannabidiol (CBD) with strong acids.
- ❖ Chemical conversion of CBD can result in a plethora of by-products and impurities.
- ❖ The chemical and pharmacological properties of delta-8 THC differ from delta-9 THC.
- ❖ Delta-8 THC, and its metabolite 11-hydroxy-delta-8 THC, have psychotropic activity.
- ❖ The US FDA has issued warnings around the safety and efficacy of delta-8 THC following an increase in adverse event notifications.

2.1 Understanding Delta-8 THC

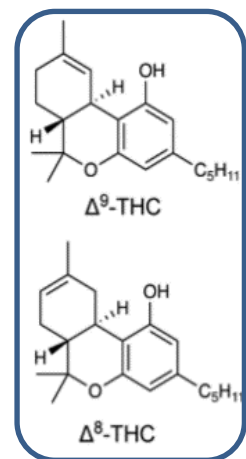
The main compound responsible for the psychotropic effect of the plant *Cannabis sativa* L. is delta-9 tetrahydrocannabinol (delta-9 THC). Due to its almost universal presence in cannabis, it is generally referred to as “THC”. However, THC exists as a group of compounds which have the same formula but variations in structure, which are called isomers in chemistry. Isomers of THC may occur naturally in the cannabis plant in differing amounts, or may be synthesised.

There is increasing attention on one isomer of THC – delta-8 tetrahydrocannabinol (delta-8 THC). This focus has in part been driven by changes in the legislative framework in key global markets, such as the introduction of the 2018 Farm Bill in the United States which removed “hemp” from the definition of “marijuana” in the U.S. Controlled Substances Act. While both hemp and marijuana refer to the *Cannabis* plant, hemp is normally differentiated by reference to the THC content of the plant material, and in the U.S. this definition is explicitly, and exclusively, to the delta-9 THC content [1]. With delta-8 THC falling outside of the definitions for hemp, there has been an upswing in products containing delta-8 THC in the U.S., and subsequently a consumer alert [2], following an increase in adverse event notifications relating to the use of delta-8 THC, issued by the Food and Drug Administration (FDA).

Varieties of *Cannabis* which fit the definitions of hemp may contain other cannabinoids outside of THC, including cannabidiol (CBD). It is possible to synthesise isomers of THC by chemically converting CBD. The legal implications associated with synthesising isomers of THC from CBD derived from *Cannabis*, whether the plant meets a local definition of hemp or not, are dependent upon the jurisdiction.

The purpose of this document is not to discuss the legalities of delta-8 THC, its synthesis or use. Instead, this document highlights the similar but unique chemical structures of delta-9 THC and delta-8 THC, and the importance of not defaulting, in the absence of evidence, to considering these isomers as equivalent in all but name.

Given the differences in the chemical and pharmacological properties between these isomers of THC, transparency in labelling by suppliers, informed decisions by prescribers, and awareness by patients, are key to ensuring patient safety and to avoid medicine confusion or medicine mistakes.



Pathways to Synthesis

Cannabis does not produce neutral cannabinoids (such as CBD, THC), but rather carboxylic acid forms of these molecules (CBDA and THCA), which then decarboxylate, usually through the application of heat and oxygen, to the neutral cannabinoids.

Not all varieties of the *Cannabis sativa* L. plant produce notable levels of THC, however even amongst those that do, the major constituent is the carboxylic acid of delta-9 THC, with generally only trace amounts of the delta-8 THC isomer. As delta-8 THC is the more thermodynamically stable of the two, there remains uncertainty as to whether this minor cannabinoid is in fact an artefact of extraction and analysis [3].

Synthesis of delta-9 THC and/or delta-8 THC can occur through electrophilic cyclization of CBD under acidic conditions [3]. While CBD can be converted to THC under laboratory conditions, the carboxylic acid form of CBD (CBDA) is not converted to the carboxylic acid form of THC (THCA) in plant tissue.

Golombek *et al.* [4] provides a detailed summary of conversion routes for CBD that have been reported in the literature. Adams *et al.* [5] first reported on acid-catalysed conversion of CBD, with the end products later confirmed by Gaoni and Mechoulam [6], who verified that treatment of CBD with hydrochloric acid resulted predominantly in delta-9 THC, while the addition of *p*-toluenesulfonic acid results in delta-8 THC. As highlighted in the Golomek review [4], acid catalysed conversion of CBD results in a broad spectrum of products, depending upon reagents and conditions used.

The safety of the reagents used and the potential by-products from this synthesis of delta-8 THC, and whether or not any post-synthesis purification is performed are a key consideration for inclusion in any medicinal product.

Psychotropicity

Delta-8 THC is psychoactive, and has been estimated in one study to be less psychoactive than delta-9 THC [7]. Metabolism of THC is well known to result in hydroxylation at C11, which has led to investigations on the psychotropic effect of the metabolites 11-hydroxy-delta-9-THC [8] and 11-hydroxy-delta-8-THC [9]. Both studies reported that the hydroxylated metabolites of the THC isomers had greater psychotropic effect than their parent molecules.

As the psychoactive effect of delta-9 THC is often an undesirable side effect in medicinal cannabis, the lower psychotropic effect for delta-8 THC reported by Hollister and Gillespie [7] may appear beneficial. However it also highlights that the isomers differ pharmacologically. The lack of evidence on the mechanisms of pharmacological action of delta-8 THC was highlighted in the 2019 World Health Organisation (WHO) technical report [10].

Delta-8 THC Medicines

In Australia, medicinal cannabis products are available if they are a registered medicine or through special access provisions of the *Therapeutic Goods Act 1989* if they are unregistered (the majority of medicinal cannabis products in Australia).

The *Therapeutic Goods (Standard for Medicinal Cannabis) (TGO 93) Order 2017* requires the identification of each active ingredient, including quantity or proportion, where it falls within a stated range. Under this Therapeutic Goods Order, where THC is present in excess of 1% of the preparation it is taken to be an active ingredient. This applies to delta-8 THC.

Given the different risk profile between isomers of THC (based on origin, potential impurity profiles, chemical properties, toxicity and pharmacological effect), transparency of labelling is an expectation on industry under the MCIA's Code of Conduct, while the MCIA encourages active and informed decisions by prescribers and ongoing and targeted research on delta-8 THC.

The MCIA believes that together these actions will contribute to patient safety.

References:

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