Australian Government
Department of Health
Therapeutic Goods Administration

Conforming with Therapeutic Goods (Standard for Medicinal Cannabis) (TGO 93) Order 2017

Version 1.3, November 2020

TGA Health Safety Regulation

Contents

Unapproved medicinal cannabis products imported into and supplied/manufactured in Australia must conform with *Therapeutic Goods (Standard for Medicinal Cannabis) (TGO 93) Order 2017* (TGO 93). TGO 93 is a standard that specifies minimum quality requirements for medicinal cannabis products.

This guidance is for manufacturers and sponsors, to assist in ensuring medicinal cannabis products conform with TGO 93. A Compliance checklist for sponsors is also available which outlines the specific criteria and paperwork required for submission to the TGA.

Responsibility for products conforming with TGO 93 rests with the sponsor. It is an offence under the *Therapeutic Goods Act 1989*, to import, export, or supply therapeutic goods that do not conform to an applicable standard.

The TGA has developed a declaration form that must be completed for **unapproved medicinal cannabis products** to declare that the product(s) conform to TGO 93. **This should be completed by the medicinal cannabis product manufacturer.**

This form should be completed prior to the supply of any new unapproved medicinal cannabis products in Australia, and also following any material change to medicinal cannabis products (including cannabis plants used in their manufacture) that were the subject of a previous declaration of conformity provided to the TGA where that change could have affected the quality of the products.

The reason for requesting that the medicinal cannabis product manufacturer complete the declaration form is that the person importing or supplying the unapproved medicinal cannabis product(s) in Australia may not be the commercial sponsor of the good (for example, a medical practitioner). The highly technical nature of TGO 93 means that this person may not be in a position to declare that the product conforms to the standard. The manufacturer of the medicinal cannabis product that has responsibility for quality control testing of the finished product is best placed to declare that the medicinal cannabis product conforms to this standard.

The manufacturer of the medicinal cannabis product(s) should submit the completed form to the person applying to access the medicinal cannabis product(s) through the available access pathways.

Please note that although the cannabis plant used in the manufacture of the medicinal cannabis product must meet the requirements of Schedule 1 of TGO 93, reduced or rotational testing of the cannabis plant used in the manufacture of the product can be carried out provided that this is justified on good manufacturing practice (GMP) grounds. For example, a manufacturer may be able to justify reducing or not conducting pesticide testing if no pesticides are used in the cultivation of the cannabis plant. Medicinal cannabis products, like any therapeutic good may be subject to testing by the TGA at any time to ensure compliance with relevant standards.

For unapproved medicinal cannabis products to be accessed via:

- **SAS and Authorised Prescriber:** The medical practitioner is required to submit this form as supportive documentation to the TGA with their notification or application, unless the sponsor has already submitted the form to the TGA on the applicant's behalf
- **Clinical trials - CTN/CTA:** The Australian clinical trial sponsor should complete the section at the end of the form to include the name of the medicinal cannabis product(s) used in the clinical trial as well as the TGA clinical trial application number and protocol number. The clinical trial sponsor is then required to submit this form as supportive documentation to the TGA with their application or notification, as applicable. In the case of a CTN involving the use of a medicinal cannabis product, the clinical trial sponsor should submit this form via email to clinical.trials@health.gov.au. In the case of a CTA involving the use of a medicinal cannabis product, the clinical trial sponsor should submit this form as part of the CTA application made to the TGA.

What TGO 93 applies to

TGO 93 applies to:

- ü any medicinal cannabis product imported into, exported from, or supplied in Australia
- ü cannabis plant used in the manufacture of medicinal cannabis products (e.g. as an ingredient or as a starting material for an extract used as an ingredient)
- ü any other ingredients used in the manufacture of medicinal cannabis products, such as excipients
- ü steps and procedures carried out in the manufacture of medicinal cannabis products

TGO 93 does not apply to medicinal cannabis products:

- û imported by a member of a group of persons visiting Australia to participate in a national or international sporting event, as described in item 4 of Schedule 5A to the *Therapeutic Goods Regulations 1990*
- û imported by a member of the military forces of another country visiting Australia for military training, as described in item 8 of Schedule 5A to the *Therapeutic Goods Regulations1990*
- û imported by a medical practitioner or member of a medical team accompanying a critically ill patient, as described in item 10 of Schedule 5A to the *Therapeutic Goods Regulations 1990*
- û imported by a member of a group of persons that includes the Head of Government or Head of State of a foreign country and senior Government officials of that country, who are visiting Australia on official business, as described in item 11 of Schedule 5A to the *Therapeutic Goods Regulations 1990*
- û that are part of the medical supplies of a marine vessel or an aircraft visiting Australia for use in treatment of a passenger or crew member, as described in item 12 of Schedule 5A to the *Therapeutic Goods Regulations 1990*
- û that are described in item 1 of Schedule 5 to the *Therapeutic Goods Regulations 1990*

What TGO 93 applies to is defined in Section 6 of TGO 93.

Commencement

TGO 93 commences the day after it is registered on the Federal Register of Legislation (section 2 of TGO 93). All medicinal cannabis products imported, exported or supplied in Australia must conform with TGO 93 from its commencement, unless you have been given a consent by the Secretary.

Interpretation

The terms used in TGO 93 are consistent with therapeutic goods legislation, and may differ in meaning from the terminology in narcotic drugs legislation (*Narcotic Drugs Act 1967* and *Narcotic Drugs Regulation 2016*).

'Act' is defined in section 4 of TGO 93 as the *Therapeutic Goods Act 1989* and 'Regulations' as the *Therapeutic Goods Regulations 1990*. Any term not defined in TGO 93 will usually take its ordinary English meaning.

European Pharmacopeia monographs

Section 7 of TGO 93 incorporates the requirements of the following general monograph of the European Pharmacopoeia as being applicable to medicinal cannabis products and ingredients:

- *Pharmaceutical Preparations (2619)*

This general monograph encompasses the requirements of specific monographs of the European Pharmacopeia for pharmaceutical raw materials (e.g. active ingredients, excipients) as well as the requirements of general texts (e.g. *Residual Solvents (5.4)*) and other general monographs of the European Pharmacopeia, including:

- *Herbal Drugs (1433)*
- *Herbal Drug Preparations (765)*
- *Herbal Drug Extracts (765)*
- *Substances for Pharmaceutical Use (2034)*
- dosage form monographs such as *Oromucosal Preparations (1807)*

Source of active ingredients and cannabinoids

All active ingredients and cannabinoids in medicinal cannabis products must be manufactured from the cannabis plant **only** (section 8 of TGO 93). This means that medicinal cannabis products cannot contain:

- the synthetic form of any cannabinoid [including, for example, the synthetic form of tetrahydrocannabinol (THC) (known as dronabinol)]
- active ingredients from any source other than the cannabis plant

Decontamination

If you decontaminate the cannabis plant—for example, by using gamma irradiation to reduce the microbial load—you must **ensure** that this does not adversely affect the quality of the medicinal cannabis product (section 9(a) of TGO 93).

Do not use ethylene oxide to decontaminate the cannabis plant (section 9(b) of TGO 93). This is in line with current guidance on the quality of herbal medicinal products. For more information, see:

- *Guideline on quality of herbal medicinal products1/traditional herbal medicinal products(EMA/CPMP/QWP/2819/00 Rev. 2)*

Identification

You must positively identify the cannabis plant used in the manufacture of medicinal cannabis products and differentiate it from potential adulterants and substitutes using each of the following identification methods (section 10 of TGO 93):

- macroscopic examination
- microscopic examination

- chromatographic procedures

These identification methods must be suitably validated and performed on every batch of the cannabis plant.

TGA guidance Identification of herbal materials and extracts relates to the identification of plant materials, such as cannabis plant, that do not have a monograph in a pharmacopoeial standard. This guidance specifies that the macroscopic, microscopic, and chemical characteristics of the plant should be compared against either:

- an authenticated reference specimen

OR

- the descriptions given in an authoritative literature source such as:
  - the United Nations Office of Drugs and Crime website: Recommended methods for the identification and analysis of cannabis and cannabis products
  - the American Herbal Pharmacopoeia monograph *Cannabis inflorescence*

Further guidance on identification testing is given in United States Pharmacopeia-National Formulary General Chapter <563> *Identification of articles of botanical origin*.

Chromatographic procedures

Chromatographic procedures are chemical tests that determine whether the characteristic chemical constituents of the plant are present in the plant.

Examples of chromatographic procedures include:

- high-performance liquid chromatography
- thin-layer chromatography
- gas chromatography

Tests may involve one or more chromatographic procedures. For example, the British Pharmacopoeia for *Holy Basil Leaf* (the dried leaves of *Ocimum tenuiflorum*) stipulates the use of macroscopic and microscopic examination as well as two thin-layer chromatography test procedures for the identification of the plant.

Chemical constituents of cannabis plant

Recognised chemical constituents of the cannabis plant include cannabinoids, such as tetrahydrocannabinols, and terpenes.

Examples of tetrahydrocannabinols include:

- delta-9-tetrahydrocannabinol (also commonly referred to as tetrahydrocannabinol, delta-9THC, or THC)
- tetrahydrocannabinolic acid (THC-acid)
- delta-8-THC
- tetrahydrocannabivarin (THCV or THV)
- 11-hydroxy-delta-9-THC

Examples of other cannabinoids include:

- cannabidiol (CBD)
- cannabidiolic acid (CBD-acid)
- cannabichromene (CBC)
- cannabinol (CBN)

Examples of terpenes include:

- beta-caryophyllene
- geraniol
- alpha-humulene
- limonene
- linalool
- myrcene

Some cannabinoids such as THC and CBD are unique to the *Cannabis* genus.

Gas chromatography can be used to confirm that cannabinoids and other characteristic terpenes are present in the cannabis plant.

Adulteration

Do not adulterate the formulated medicine or any of its ingredients with undeclared substances. Tobacco, calamus and synthetic cannabinoids are notable examples of adulterants (section 11 of TGO 93).

The motivation for adulterating a product is irrelevant—the presence of any substance extraneous to the formulation (such as undeclared substances)—will be considered to amount to adulteration for the purposes of TGO 93.

'Incidental minor excipients' are not considered adulterants. These are defined in section 4 of TGO 93 as:

- an excipient or processing aid in the manufacture of ingredients for medicinal cannabisproducts

OR

- a processing aid in the manufacture of medicinal cannabis products

Tests

TGO 93 specifies tests and assay limits in section 12 of TGO 93.

How to validate tests

For guidance on the principles and practice of validating tests:

- *ICH Harmonised Tripartite Guideline Validation of Analytical Procedures: Text andMethodology Q2 (R1)*.

Cannabis plant tests

The cannabis plant you use must comply with the limits specified in Schedule 1, in addition to being positively identified as described in section 10 of TGO 93. The limits for the parameters apply **on a dried basis**, with the exception of the test for foreign matter). It may be appropriate to carry out additional tests to those specified in TGO 93 in certain circumstances.

Sample size and preparation guidance

Choose a sample size that is representative of the batch. For guidance on sample sizes and how to prepare herbal plant material for analysis, see:

European Pharmacopoeia method of analysis *Herbal Drugs: Sampling and Sample Preparation (2.8.20)*

Specified tests

You must determine whether the cannabis plants used to manufacture the medicinal cannabis products meet the requirements of Schedule 1.

The following parameters are specified in Schedule 1:

1. aflatoxins
2. foreign matter
3. heavy metals (arsenic, cadmium, lead and mercury)
4. ochratoxin A
5. pesticides
6. total ash

The tests in Schedule 1 are standard pharmacopoeial tests applied to the cannabis plant used in the manufacture of medicinal products. For more information, see:

- European Pharmacopoeia general monograph *Herbal Drugs (1433)*
- *Guidance on Specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products/Traditional Herbal Medicinal Products(CPMP/QWP/2820/00 Rev 2)*.

Every batch must comply

Every batch of your medicinal cannabis product must be manufactured from cannabis plants that meet the requirements of Schedule 1. Generally, we expect all tests to be carried out on a routine basis to ensure that if a sample was tested by the TGA it would meet TGO 93 requirements.

However, in accordance with good manufacturing practice (GMP) considerations, you may perform reduced or rotational testing for non-critical tests provided that you are able to justify this reduced or rotational testing. For example, you may be able to justify reducing or not conducting pesticide testing if no pesticides are used in the cultivation of the cannabis plant.

Alternative tests

You do not have to use the methods specified in Schedule 1 to test the cannabis plant. You could use:

- equivalent methods in established pharmacopoeia, including the United States Pharmacopoeia-National Formulary
- suitably validated in-house or literature (non-pharmacopoeial) tests that are suitable for the intended purpose

However, in the event of a dispute, the methods of analysis specified in TGO 93 are the official methods.

Additional tests

In addition to testing the parameters specified in Schedule 1, consider performing additional tests on the cannabis plant from the general monograph on *Herbal Drugs (1433)*, where such tests are warranted.

For example:

- water or loss on drying:
  - Consider performing tests for the cannabis plant in relation to water or loss on drying with appropriate limits to ensure that the cannabis plant does not contain excessive moisture that could facilitate the growth of microorganisms
- Radioactivity
  - Consider performing tests for the cannabis plant in relation to radioactive contamination if the plant is grown in an area with potential for radioactive contamination, e.g. the Chernobyl region.

Assay of active ingredients in the product

You need to measure the contents of the active ingredients. The actual quantity of active ingredients must be within a specified range of the stated quantity [section 12(2) of TGO 93]. This range applies at both release and end of shelf-life.

Active ingredient definition

An active ingredient is a therapeutically active component in the medicine's final formulation that is responsible for its physiological or pharmacological action (section 4 of TGO 93). In addition, the following ingredients are considered to be active ingredients in section 4(2) of TGO 93 for the purposes of TGO 93:

- any tetrahydrocannabinol (including any corresponding acid) greater than or equal to 1.0% w/w or w/v of the product
- any other cannabinoids (including any corresponding acid) greater than or equal to 2.0% w/w or w/v of the product

Corresponding acids

The term 'corresponding acid' is used because some cannabinoids such as THC and CBD ordinarily exist in the cannabis plant in the form of their corresponding acid, namely THC-acid and CBD-acid respectively. These acids form THC and CBD as a result of decarboxylation during storage or heating.

It is common practice to express the contents of cannabinoids in the cannabis plant as the total of cannabinoid and corresponding acid. For example, total THC is the sum of THC and THC-acid and total CBD is the sum of CBD and CBD-acid. The assay should be performed with reference to these total sums.

Assay method

No particular test method is prescribed for calculating the average content of each active ingredient in accordance with section 12(2) of TGO 93. The assay method you use will depend on the active ingredient, the dosage form and the formulation of the product. You can use any suitably validated test method.

Examples of literature assay methods can be found in:

- Monograph Cannabis Flos Version 7.1 (November 28, 2014)_40953, Dutch Office ofMedicinal Cannabis
- Recommended methods for the identification and analysis of cannabis and cannabis products, United Nations Office on Drugs and Crime.

Stated content

The assay limits are specified in relation to the stated content of each active ingredient. 'Stated content' is defined in section 4 of TGO 93. 'Stated content' means the quantity or proportion of each active ingredient:

- specified on the label, if we have approved an application under section 25 of the *Therapeutic Goods Act 1989*
- disclosed in an application made under section 19 of the *Therapeutic Goods Act 1989*, whether or not the quantity or proportion is specified on the label
- disclosed in an application made under regulation 12A of the Regulations, whether or not the quantity or proportion is specified on the label
- purported to be present in a medicinal cannabis product that is dispensed, or extemporaneously compounded, for a particular person for therapeutic application to that person, in the manner mentioned in item 6 of Schedule 5 to the *Therapeutic Goods Regulations 1990*
- notified to be present for the purpose of clinical trials as described in item 3 of Schedule 5Ato the *Therapeutic Goods Regulations 1990*

Assay limits for various dosage forms

You need to test the contents of the active ingredients in medicinal cannabis products. The assay limits for these tests are specified at section 12(2) of TGO 93 and will differ depending on the dosage form of products, specifically:

- herbal final form
- tablets and capsules

- other dosage forms

Herbal dosage form

When the product is in herbal final form (section 12(2)(a) of TGO 93), such as sachets of cannabis leaf material, each active ingredient, together with any corresponding acid, in a representative sample must be in the range of 80.0–120.0% of the stated content of that active ingredient.

Tablets or capsules

When the product is in tablet or capsule form (section 12(2)(b) of TGO 93), the average content of each active ingredient, together with any corresponding acid, as determined from a pooled sample of not fewer than 20 tablets or capsules, must be in the range of 90.0–110.0% of the stated content of that active ingredient.

Tablets or capsules on the ARTG

Medicinal cannabis products in tablet or capsule form that are registered on the ARTG must comply with the assay limits in TGO 101, which are tighter than those in TGO 93 (section 12 note).

Other dosage forms

For any other dosage form (for example, oromucosal spray) (section 12(2)(c) of TGO 93), the content of each active ingredient, together with any corresponding acid, in a representative sample must be in the range of 90.0–110.0% of the stated content of the active ingredient.

Other relevant standards

In addition to TGO 93, medicinal cannabis products must also conform with any other applicable therapeutic goods orders.

You must comply with any applicable Therapeutic Goods Order.

Examples of applicable therapeutic goods orders include:

- for all medicines: Therapeutic Goods Order No. 77 *Microbiological Standards for Medicines*
- for tablets and capsules registered on the ARTG: *Therapeutic Goods (Standard for Tablets, Capsules and Pills) (TGO 101) Order 2019*

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Laboratories Branch; Pharmacovigilance and Special Access Branch; Regulatory Guidance Team	March 2017
V1.1	Updated to clarify content	Pharmacovigilance and Special Access Branch	July 2018
V1.2	Updated to amend name	Pharmacovigilance and Special Access Branch	May 2019
V1.3	Minor updates to reflect CTA name change	Biological Science Section	November 2020

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au

D17-76046