MEDICINAL CANNABIS AGENCY

MINISTRY OF HEALTH
MANATŪ HAUORA

GUIDELINE ON THE REGULATION OF MEDICINAL CANNABIS IN NEW ZEALAND

PART 2

Information for New Zealand Manufacturers and Packers

EDITION 2.0
February 2022

New Zealand Government

Citation: Ministry of Health. 2020. *Guideline on the regulation of medicinal cannabis in New Zealand: Part 2 Information for New Zealand Manufacturers and Packers*. Wellington: Ministry of Health.

Published in April 2020 by the Ministry of Health
PO Box 5013, Wellington 6140, New Zealand

ISBN 978-1-98-859779-9 (online)
HP 7386

Contents

Section 1: Introduction

This guidance document is **Part 2: Information for New Zealand Manufacturers and Packers** of the *Guideline on the Regulation of Medicinal Cannabis in New Zealand*.

Here we provide prospective manufacturers and packers of medicinal cannabis products (as per the definition of a medicinal cannabis product set out in the Misuse of Drugs (Medicinal Cannabis) Regulations 2019) with relevant information about:

- the Licence to Manufacture Medicines and the Licence to Pack Medicines under the Medicines Act 1981
- how to comply with the New Zealand Code of Good Manufacturing Practice for Manufacture and Distribution of Therapeutic Goods.

We recommend you read Parts 1 to 5 of the Guideline in full. For detailed information about how to apply for a Medicinal Cannabis Licence, see **Part 4: Guidance for Applicants for a Medicinal Cannabis Licence** of the *Guideline on the Regulation of Medicinal Cannabis in New Zealand*.

Section 2: Background on regulatory settings

2.1 Medicinal Cannabis Licence

A **Medicinal Cannabis Licence** authorises the licence holder to carry out one or more types of 'activity'. The 'possession for manufacture' activity must be specified on the licence if the holder intends to extract a cannabis-based ingredient, manufacture a medicinal cannabis product, or perform laboratory testing.

Refer to **Part 4: Guidance for Applicants for a Medicinal Cannabis Licence** of the *Guideline on the Regulation of Medicinal Cannabis in New Zealand* for information about Medicinal Cannabis Licences.

2.2 Minimum quality standard for medicinal cannabis products

All medicinal cannabis products intended for use by patients (including cannabidiol (CBD) products) must meet the minimum quality standard for medicinal cannabis. Product assessments are the method used to verify whether a product meets the minimum quality standard.

For information about the minimum quality standard and product assessments, go to: the minimum quality standard page on the Medicinal Cannabis website.

2.3 Licences issued under the Medicines Act 1981

If you hold a Medicinal Cannabis Licence and wish to manufacture a medicinal cannabis product for patients to use, you will also need to hold a **Licence to Manufacture Medicines** issued under the Medicines Act 1981. This licence permits the holder to manufacture, test, pack and label medicines.

If you hold a Medicinal Cannabis Licence but your manufacturing activities are limited to repacking products that a GMP certified facility has manufactured and that have been verified as meeting the medicinal cannabis minimum quality standard, you need a **Licence to Pack Medicines** under the Medicines Act 1981 instead of a Licence to Manufacture Medicines. This licence permits the holder to pack and label medicines only.

When you have starting materials for export, that require further industrial processing, you do not need to comply with the requirements of GMP. Neither a Licence to Manufacture Medicine nor a Licence to Pack Medicine would be required in this instance. Alternatively, if your starting material for export is supplied as bulk or as a finished packed product then you would need to comply with the requirements of GMP and a Licence to Manufacture or Licence to Pack will be required.

To obtain a Licence to Manufacture Medicines or a Licence to Pack Medicines, you must be able to demonstrate that you comply with the New Zealand Code of Good Manufacturing Practice for Manufacture and Distribution of Therapeutic Goods (the GMP Code).

For more information about licences to manufacture and/or pack medicines, contact the Medsafe's Compliance Branch by sending an email to the gmp@health.govt.nz inbox. Fees for Licenses are included in the schedule of fees payable under the Medicines Act 1981.

2.4 Licence to import or export controlled drugs

You must have a licence to commercially import or export controlled drugs, including medicinal cannabis products.

For exports, the importing country must provide a 'licence to import' before Medicines Control can issue a licence to export controlled drugs.

The application fee for a licence to import or export controlled drugs is $194.22 including goods and services tax (GST) for each consignment. A licence is required for each consignment, but each consignment may contain up to four preparations or products.

Up to 30 working days is required to process an application for an import or export licence.

For further information or to receive an application form for a licence to import or export controlled drugs, contact the Advisor (Controlled Drugs), Medicines Control, on 04 816 2018 or at medicinescontrol@health.govt.nz.

Note: Import and export licences are not required for cannabis-based ingredients and medicinal cannabis products (dosage products) that meet the definition of a CBD product. However, requirements under the Medicines Act 1981 and Medicines Regulations 1984 continue to apply refer to CBD product information on Medicinal Cannabis Agency website.

Section 3: Good Manufacturing Practice – complying with the GMP Code

To obtain a Licence to Manufacture Medicines and/or a Licence to Pack Medicines under the Medicines Act 1981, you must demonstrate that you comply with the GMP Code. An auditor will conduct a GMP audit of the facility and determine whether you comply, as part of the licence assessment.

3.1 The GMP Code

The GMP Code consists of:

- PE 009-14 (Part I) PIC/S GMP Guide (Part I: Basic Requirements for Medicinal Products)
- PE 009-14 (Part II) PIC/S GMP Guide (Part II: Basic requirements for active pharmaceutical ingredients)
- PE 009-14 (Annexes).

PE 009-14 (Part I) PIC/S GMP Guide (Part I: Basic Requirements for Medicinal Products) provides guidance on manufacturing and packing finished medicinal cannabis products.

PE 009-14 (Part II) PIC/S GMP Guide (Part II: Basic requirements for active pharmaceutical ingredients) provides guidance on manufacturing cannabis-based ingredients.

PE 009-14 (Annexes) provides additional guidance for specific product types and more detail for specific topic areas. Use these annexes together with Part I or Part II.

Table 1 lists the annexes relevant to medicinal cannabis products and gives examples of the types of products that these annexes may apply to.

Table 1: Annexes in the GMP Code relevant to medicinal cannabis products

Annex number	Annex title	Product types annex may apply to
7	Manufacture of herbal medicinal products	Flos, herbal tinctures, herbal powders
8	Sampling of starting and packaging materials	All product types
9	Manufacture of liquids, creams and ointments	Liquids, creams and ointments
10	Manufacture of pressurised metered dose aerosol preparations for inhalation	Pressurised metered dose aerosol preparations for inhalation
11	Computerised systems	All products
12	Use of ionising radiation in the manufacture of medicinal products	Any products using ionising radiation to reduce bioburden
13	Manufacture of investigational medicinal products	Clinical trial products
15	Qualification and validation	All products
19	Reference and retention samples	All products

Annex number	Annex title	Product types annex may apply to
20	Quality risk management Note: This is a voluntary annex.	All products

For the GMP Code and its annexes, go to the regulatory guidelines on the Medsafe website.

3.2 How to find out more about the GMP Code

If your organisation is not familiar with the GMP Code, you may wish to seek help from a therapeutic products consultant. For a list of consultants who have self-notified refer to the regulatory consultants list on the Medsafe website.

> **Note:** Before engaging the services of any particular consultant, you should evaluate whether their services are suitable for your requirements.

Section 4: When to start implementing the GMP Code in the manufacturing process

Which step in the manufacturing process is your starting point for implementing the GMP Code will vary depending on the dosage form of the medicinal cannabis product and the manufacturing process you are using. You should conduct a comprehensive risk assessment to support your choice of starting point.

In the risk assessment, first identify the controls for each manufacturing step that could impact product quality. Then document a comprehensive strategy for controlling risks to product quality. This strategy should outline the rationale behind your choice of starting point for implementing the GMP Code.

You should document your risk assessment and have it available for review if requested during the assessment of your application for a Licence to Manufacture Medicines and/or a Licence to Pack Medicines.

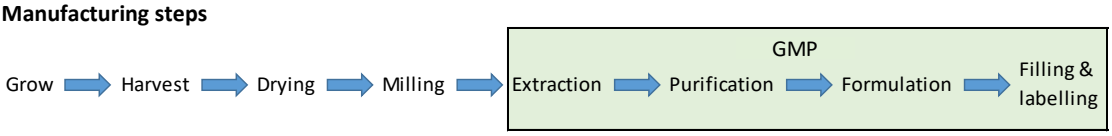
For guidance on how to complete risk assessments, see Annex 20 of the GMP Code.

The examples below are designed to help you work out your own starting point for applying the GMP Code across various dosage forms.

> **Note**: These examples are intended as general guidance only. You should always complete a comprehensive risk assessment for your specific product and manufacturing process to work out your starting point for implementing the GMP Code.

Example 1: Dosage form – cannabis oil formulation

Manufacturing steps



This manufacturer's starting point for implementing the GMP Code is at extraction.

In this example, the rationale for implementing the GMP Code at extraction is based on the importance of this step in separating the desirable cannabinoids from the plant matrix. This step has a direct impact on the finished product quality.

This manufacturer should continue implementing the GMP Code during all the following manufacturing steps to reduce risks that could impact product quality. Examples of such risks are the risk of introducing contaminants and the risk of there being excess solvents left over from the extraction process.

Example 2: Dosage form – milled cannabis in a hard-shell capsule

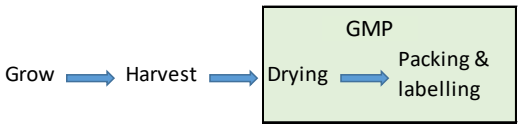
Manufacturing steps

This manufacturer's starting point for implementing the GMP Code is at drying.

The rationale for implementing the GMP Code at the drying step is to ensure moisture levels do not have an adverse impact on product quality. GMP should also be implemented during subsequent steps to reduce risks that could impact product quality.

Example 3: Dosage form – dried cannabis flower

Manufacturing steps



This manufacturer's starting point for implementing the GMP Code is at drying.

The rationale for implementing the GMP Code at the drying step is to ensure moisture levels are controlled to prevent mould proliferation. GMP should also be implemented during the subsequent step to reduce risks that could impact product quality.

Section 5: How to prepare for an audit against the GMP Code

This section provides general guidance to help you prepare for an audit against the GMP Code. The audit is part of the assessment for a Licence to Manufacture Medicines or a Licence to Pack Medicines under the Medicines Act 1981.

Please note that even if you implement the systems described in this section, it may not be enough in all cases to achieve full compliance with the GMP Code. You should develop a good understanding of all aspects of the GMP Code **before** you apply for a licence.

5.1 Quality management system

Design and implement a quality management system (QMS) to cover all activities involved in manufacturing and packing medicinal cannabis products.

The QMS will include a documentation system in which processes are clearly defined using standard operating procedures, specifications and batch records.

A robust change control system is one of the key components of any QMS. This will ensure that manufacturers assess all process changes for their impact on product quality before implementation, apply appropriate controls and identify any requirements for requalification and revalidation.

Changes that have the potential to affect product quality may include, for example, changes to starting material, packaging materials, equipment, manufacturing processes, test methods, batch size, facilities, and key personnel.

For more information about QMS systems, see Part I of the GMP Code.

5.2 Premises and equipment

The GMP audit will assess all facilities and equipment you use to manufacture, store and test medicinal cannabis products. Before the audit begins, you should set up all facilities and equipment so that they are ready to use.

You should also have completed the qualification of equipment and facilities and documented it before the audit, in line with Annex 15 of the GMP Code (Qualification and validation). Your qualification documents and any supporting data should be available for review.

You should have established cleaning, calibration and preventative maintenance programmes, with procedures and records available for review at the audit.

You must also have a separate audit to assess security for facilities where you intend to manufacture medicinal cannabis products. For information on security requirements and the security site inspection, see security of cannabis on the Medicinal Cannabis Agency's website.

5.3 Product development must be complete

By the time of the audit, you should have developed your medicinal cannabis product to a point where you have:

- defined a manufacturing batch
- developed specifications for the raw materials, finished product and primary packaging components
- established the manufacturing process and written standard operating procedures
- established the control points and critical parameters for the process
- finalised batch manufacturing and packing records.

5.4 Process validation

Process validation ensures all manufacturing processes for a medicinal cannabis product meet the predefined acceptance criteria. Ideally you should have completed all process validations before the audit against the GMP Code and have the associated documents and supporting data available for review.

Process validation is different to the trials and testing completed during product development. By the time you are ready to carry out process validation, you should not need to make any changes or adjustments.

For guidance on process validation, see Annex 15 of the GMP Code (Qualification and validation).

> **Note:** Where you have manufactured medicinal cannabis product before Medsafe has issued your Licence to Manufacture Medicine, you can only use that product for laboratory testing and not for patient use. Concurrent process validation may be acceptable when a GMP audit has already confirmed a site is operating in accordance with the GMP Code. Product manufactured to support concurrent validation may subsequently be distributed following successful completion of the validation studies. Conditions would be placed on a Licence to Manufacture Medicines to this effect.

If you make any process or equipment changes after validation, you should control, assess and document them using the change control process in the QMS. The impact of the change on the process validation should be included in the assessment and re-validation might be required.

5.5 Site master file

A site master file (SMF) is a document that provides clear and specific information about the manufacturing operations carried out at a given site. A SMF helps you to prepare for the application audit and is a useful tool for you to use to check you have considered all aspects of the GMP Code when establishing the QMS.

For guidance on the information to include in an SMF, go to the Pharmaceutical Inspection Convention Scheme website.

Section 6: The audit process

The audit process involves the following seven steps.

6.1 Lodging the application

After Medsafe receives your application for a Licence to Manufacture Medicines or a Licence to Pack Medicines, an auditor will review the application. The auditor will provide you with a Pre-Audit Questionnaire to complete and may request an SMF or other information from your QMS to verify that you have key systems in place before a GMP audit is schedule.

6.2 Arranging the audit date

The auditor contacts you to arrange a date for the audit. The audit could take less than a day for a very small site or several days for a larger site.

6.3 Carrying out the GMP audit

During the audit, the auditor will identify any discrepancies between your system and the requirements of the GMP Code and discuss them with you. The auditor will summarise all deficiencies at a meeting with company management at the end of the audit so you can start rectifying them straight away.

6.4 Preparing the audit report

The auditor prepares the audit report, setting out any identified deficiencies and making a license recommendation that results in:

- issuing a licence, or
- deferring a decision until you have rectified key deficiencies, or
- declining the application.

6.5 Opportunity to respond

If the auditor has identified any deficiencies, these deficiencies will be communicated to key personnel of the company that attended the audit closing meeting. You may start preparing the audit responses and explain how you have addressed each deficiency even before the audit report is issued. It is important when planning your corrective and preventative actions to consider the underlying cause of the deficiency rather than just the example identified at the audit.

Your response should include:

- a description of the corrective and preventative action you have planned or taken
- the date you completed the corrective and preventative action or plan to complete it
- evidence of completion (for example, photographs or copies of amended documents).

6.6 Auditor reviews response

The auditor will review your response and the evidence you provide. They may request further information.

6.7 Medsafe issues licence

Medsafe will issue a licence once it is satisfied the site meets the requirements of the GMP Code. The time it takes to reach this step depends on the findings of the audit and how well your response addresses any deficiencies.

> **Note:** The audit is a rigorous process and it is not uncommon for an organisation to require more than one audit before Medsafe issues a licence. If Medsafe decides to defer issuing a licence after the second on-site audit, and further audits are needed, you may need to lodge a new application and pay a further application fee.

Section 7: Responsibilities of licence holders

The holder of a Licence to Manufacture Medicines or a Licence to Pack Medicines under the Medicines Act 1981 has responsibilities including the following.

7.1 Comply with licence conditions

You must comply with the scope of manufacturing and/or packing activities specified on your licence. This scope may include the types of medicinal cannabis products (dosage forms) or specific products that you can manufacture.

The licence will also specify the location or locations where you can carry out these activities.

If you intend to make products or complete activities that are outside the scope of your licence, you will first need to apply to Medsafe (by emailing GMP@health.govt.nz) to amend your licence. Medsafe will assess the amendment you are proposing and may require you to have a targeted onsite audit or a desktop audit to evaluate the amendment.

7.2 Notify Medsafe of any changes you intend to make

You must notify Medsafe (by emailing GMP@health.govt.nz) of any changes you intend to make to the responsible persons recorded on your licence or to the products that you will make. You must also notify Medsafe of any major changes you intend to make to the facility, equipment or manufacturing operations.

Medsafe may need to evaluate some changes before you implement them. It may require you to have a targeted audit of any major changes to complete that evaluation.

Where it is necessary to modify a condition on your licence because of your intended change, you must also apply for a licence amendment.

7.3 Maintain validation of process

You must manage any changes to the manufacturing process through the change control system of your QMS. You may need to repeat the process validation to demonstrate the change has not altered the reproducibility of the process. Auditors will review your process validation documents as part of ongoing audits to assess your compliance with the GMP Code.

7.4 Have periodic audits against the GMP Code

Periodic audits will assess whether you are continuing to comply with the GMP Code. The frequency of these audits could be anywhere between six months and three years, depending on

the type of products you are manufacturing and your compliance history. An auditor will contact you to arrange a suitable time for each audit when it is due.