Australian Government
Department of Health
Therapeutic Goods Administration

Medicinal cannabis manufacture

Technical guidance on the interpretation of the PIC/S Guide to GMP

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TGA Health Safety Regulation

Contents

About this guidance

This guidance is for manufacturers of medicinal cannabis products. It outlines and provides information on:

- manufacturing license and certification requirements
- differences between Therapeutic Goods Administration (TGA) and Office of Drug Control (ODC) requirements
- TGA interpretation and expectations for compliance with specific sections of the current PIC/S Guide to Good Manufacturing Practice (GMP) for Medicinal Products (PIC/S Guide to GMP)

This information is provided for guidance only and has been developed on the basis of current knowledge of the subject matter. It should not be relied upon to address every aspect of the relevant legislation.

If you have further questions, or you require further clarification of a particular requirement, you can email your questions to the Manufacturing Quality Branch.

Medicinal cannabis products

In 2016 the Australian Government amended the *Narcotic Drugs Act 1967* to allow the cultivation and production of cannabis for medicinal purposes.

The *Narcotic Drugs Act 1967* gives effect to the United Nations *Single Convention on Narcotic Drugs 1961* (the Single Convention) requirements on cultivation, production of cannabis and the manufacture of narcotic drugs. Existing supply pathways (such as those under the *Therapeutic Goods Act 1989*) apply to all medicinal cannabis products cultivated or manufactured under the *Narcotic Drugs Act 1967*.

The *Narcotic Drugs Act 1967* defines 'medicinal cannabis product' to mean a product, including but not limited to, a substance, composition, preparation or mixture, that:

a. includes, or is from, any part of the cannabis plant; and

b. is for use for the purposes of curing, or alleviating the symptoms of, a disease, ailment or injury

The Office of Drug Control (ODC) has more general information regarding medicinal cannabis.

Manufacturing

For medicines, biologicals and other therapeutic goods, manufacture includes, but is not limited to, any of the following:

- production
- processing
- assembling
- packaging
- labelling
- storage
- sterilising
- testing
- release for supply

Section 3 of the *Therapeutic Goods Act 1989* contains a full definition.

For further information please see Manufacturing medicines.

Roles and responsibilities

It is your responsibility to ensure you are compliant with all relevant legislation. Failure to comply may result in sanctions and penalties from the relevant federal or local government agency.

Medicinal cannabis is subject to the *Therapeutic Goods Act 1989* as well as the *Narcotic Drugs Act 1967*, which are administered by the Australian Government Department of Health (through the TGA and ODC respectively).

State and Territory health departments also have requirements regarding how controlled substances, including medicinal cannabis, may be authorised for use in their jurisdictions.

For more information, contact your local State or Territory health department.

Role of the TGA

The TGA administers the *Therapeutic Goods Act 1989* and regulates the quality, safety and efficacy of medicines as well as access to medicines that have not been approved for general use (unapproved therapeutic goods).

The TGA is also responsible for issuing Australian manufacturing licences and overseas manufacturing certification and clearances.

The TGA has developed a series of medicinal cannabis guidance documents to assist patients and health professionals, particularly those who prescribe medicinal cannabis in Australia under current access pathways.

Regulation of medicinal cannabis

Medicinal cannabis products are not included in the Australian Register of Therapeutic Goods (ARTG) unless registered. For a product to be subsidised through the Pharmaceutical Benefits Scheme (PBS), it also needs to be included in the ARTG.

Most medicinal cannabis products can only be accessed through access pathways available for **unapproved therapeutic goods**:

- the authorised prescriber scheme
- the Special Access Scheme (SAS)
- clinical trials in certain circumstances

Unapproved therapeutic goods are those goods not included in the ARTG, but are available through the special access pathways.

When medicinal cannabis is included in the ARTG, it is classified as a 'registered' prescription medicine.

Classification in the Poisons Standard

Classification is based on how medicinal cannabis ingredients are controlled through the Poisons Standard. Ingredients from medicinal cannabis are included in either schedules 4 (prescription only), 8 (controlled drug) or 9 (prohibited drugs) of the current Poisons Standard.

Role of the ODC

The Office of Drug Control administers the *Narcotic Drugs Act 1967* and regulates controlled substances to prevent diversion and illicit use.

The ODC regulates and provides advice on the cultivation, production, import and export of controlled and narcotic drugs including medicinal cannabis, in accordance with Australia's obligations under international drug conventions. This also includes the fit and proper persons requirements, security and inspections and controlling the import and export of narcotics.

In addition, the ODC regulates how much of a particular drug may be obtained and used in Australia. Australia may not import, cultivate or manufacture controlled drugs in excess of these requirements.

Differences between TGA and ODC legislation

Terminology and definitions used under the *Therapeutic Goods Act 1989* can differ from those used in the *Narcotic Drugs Act 1967*. The same word can have different meanings in the two different Acts.

For example:

- In the context of the *Therapeutic Goods Act 1989*, '*production*' refers to the preparation of an active pharmaceutical ingredient or a finished medicinal product. As such, '*production*' is considered a subset of '*manufacture*'.
- In the context of the *Narcotic Drugs Act 1967*, '*production*' refers exclusively to the harvesting of the specified plant parts, separating resin from plant by physical/water extraction (e.g. physical separation of the cannabis flowers from the cannabis plant, physical separation of the trichomes from the cannabis flowers or cannabis plant such as sieving, ice water separation). The plant or separated resin might then undergo a processing step (e.g. solvent extraction) which is termed '*manufacture*'. As such, '*production*' is an initial step that is usually followed by '*manufacture*'.

More information regarding TGA definitions used in relation to the manufacture of medicinal cannabis can be found at:

- acronyms and glossary on the TGA website
- the glossary of the PIC/S Guide to GMP

Manufacture of medicinal cannabis

If you want to become involved in the manufacture of medicinal cannabis, you should ensure that you have the relevant:

- approvals
- licences or GMP certification or clearance
- permits under each of the relevant legislative frameworks.

This includes relevant state or territory government licences or approvals.

You must consider:

- a manufacturing licence under the *Therapeutic Goods Act 1989* (if the manufacturer resides in Australia) **or** GMP certification or clearance (if the manufacturer resides overseas)
- a manufacturing and cultivation licence and associated permits under the *Narcotic Drugs Act 1967*
- relevant state or territory government licences or approvals

You may need TGA and ODC manufacturing licences

There are **two licences** that may be required if you are manufacturing medicinal cannabis **in Australia**. These serve different purposes and operate under different legislation:

- Licence to manufacture therapeutic goods (GMP) issued by the TGA

and/or

- Narcotic manufacture licence issued by the ODC

A GMP licence focuses on quality, whereas the narcotic manufacture licence specifies what drug may be produced and in what quantities.

A GMP licence **does not** remove the requirement for a narcotic manufacture licence and vice versa.

Table 1: Licences required for manufacturing medicinal cannabis products in Australia

Licence name	Issued under	Regulator	Contact
Licence to manufacture therapeutic goods (GMP)	*Therapeutic Goods Act 1989*	Therapeutic Goods Administration (TGA)	Email: gmp@tga.gov.au Website: TGA website
Narcotic manufacture licence	*Narcotic Drugs Act 1967*	Office of Drug Control (ODC)	Email: dcs@health.gov.au Website: ODC website

TGA licencing and certification requirements

The TGA requires you to hold either:

- a current licence to manufacture therapeutic goods (GMP) (if manufacturer is based in Australia)

OR

- be covered by a current GMP clearance or certification (if manufacturer is based overseas)

Australian manufacturing licences and overseas GMP certification guidance provides more information about the process for applying for a manufacturing licence or GMP certification.

Licence to manufacture therapeutic goods (GMP)

A licence issued under the *Therapeutic Goods Act 1989* regulates matters such as quality and compliance with standards for activities such as:

- manufacture of an Active Pharmaceutical Ingredient (API)
- market authorisation
- production, processing, assembling, packaging, labelling, storage, sterilisation, testing, release for supply
- clinical trials

You need a licence to manufacture therapeutic goods for both medicinal cannabis products included in the ARTG as a prescription medicine and for medicinal cannabis products that are unapproved therapeutic goods, available through the access pathways.

If you have been granted a licence to manufacture therapeutic goods under the *Therapeutic Goods Act 1989*, you are likely to **also need** a licence to manufacture narcotic drugs under the *Narcotic Drugs Act 1967*.

Inspections

Upon receiving an application for a GMP licence in Australia, we typically conduct an on-site inspection within 3 months if the manufacturing site is ready. The time from inspection to licensing will vary depending on how quickly/effectively the manufacturing site addresses any deficiencies identified during the inspection.

You can find more information on the process at Manufacturer inspections.

GMP clearance and certification for overseas manufacturers

Only Australian manufacturing sites can obtain a manufacturing **licence**.

For overseas manufacturers of medicines, sponsors will need to obtain GMP **clearance**. This can be done through three different pathways:

- Mutual Recognition Agreement (MRA) desktop assessment
- Compliance Verification (CV) desktop assessment
- TGA on-site inspection (GMP certification)

GMP certification is usually only requested if it is not possible to obtain GMP clearance via the MRA or CV pathways (for example, due to lack of evidence). GMP certification applications are required to be submitted by the Australian sponsor or an agent acting on the Australian sponsor's behalf.

Australian manufacturing licences and overseas GMP certification guidance provides more information about the process for applying for a manufacturing licence or GMP certification.

Other TGA manufacturing requirements

PIC/S Guide to GMP

All manufacture of medicinal cannabis products must also be in compliance with the most current PIC/S Guide to GMP. More detailed information about the PIC/S Guide to GMP can be found below.

Therapeutic Goods (Standard for Medicinal Cannabis) (TGO 93) Order

A medicinal cannabis product supplied in Australia needs to conform with the Therapeutic Goods (Standard for Medicinal Cannabis) (TGO 93) Order unless synthetically prepared (not manufactured from natural origins).

The manufacturer is required to review their raw material and finished product specifications against the requirements of TGO 93.

If you are satisfied that your unapproved medicinal cannabis product(s) meet the requirements of the standard, you should complete the declaration form available on the TGA website to declare that your medicinal cannabis product(s) meets this standard.

The TGA may ask for a representative certificate of analysis for review to ensure compliance with TGO 93. Medicinal cannabis products, like all therapeutic goods, may be subject to testing by the TGA to confirm compliance with applicable standards.

The TGA has published a guidance document on applying the requirements set out in Therapeutic Goods Order No. 93 (Standard for Medicinal Cannabis) TGO 93.

Marketing authorisation

If you intend for your medicinal cannabis product to be included on the ARTG as a prescription medicine, then you must consider marketing authorisation requirements.

The Australian Regulatory Guidelines for Prescription Medicines (ARGPM) contains further information about marketing authorisation requirements.

Data management and data integrity

TGA has specific guidance relating to data management and data integrity. Refer to: Data Management and Data Integrity (DMDI) Guidance

Exemptions associated with the access pathways

SAS or authorised prescriber scheme

You may be exempt from holding a licence to manufacture and comply with GMP if you meet the exemption(s) under Schedule 8 of the *Therapeutic Goods Regulations 1990*.

Clinical trials

In the clinical trial space, there are exemptions from requiring a licence to manufacture therapeutic goods, but they must comply with GMP. This is the requirement of the ICH Guideline for Good Clinical Practice.

Pharmacists manufacturing medicinal cannabis products for supply in clinical trials are required to hold a licence to manufacture therapeutic goods and comply with GMP unless they meet the exemption(s) under Schedule 7 of the *Therapeutic Goods Regulations 1990*.

In addition to Schedule 7, there are certain persons or goods exempt from holding a manufacturing licence issued by the TGA:

- pharmacists who manufacture goods in a pharmacy where the pharmacist practices and the pharmacy is open to the public and the goods are supplied from those premises (other than by wholesale) i.e. to individual patients (item 2, Schedule 8, *Therapeutic Goods Regulations 1990*)
- pharmacists employed by a public hospital or public institution who manufacture goods for supply to patients in hospitals/public institutions in the same State or Territory (item 3, Schedule 8, *Therapeutic Goods Regulations 1990*)

ODC licencing requirements

A licence issued under the *Narcotic Drugs Act 1967* regulates the quantities and types of drugs manufactured in order to manage national stock levels, ensuring accumulation of the drug does not occur, and that the manufacture is consistent with the requirements of the Single Convention. Matters will also include examination of the probity of licence holders and the security of the facilities.

Narcotic manufacture licence

A narcotic manufacture licence is required under the *Narcotic Drugs Act 1967* for any or all of the following activities:

- obtaining an **extract** (including tinctures) from cannabis or from cannabis resin
- separating, or obtaining cannabinoids (e.g. cannabidiol, THC) from the **extract**
- converting or transforming cannabinoids present in the **extract** into another drug

A narcotic manufacture licence does not cover matters such as:

- cultivation or production of cannabis (a licence for this activity under the *Narcotic Drugs Act 1967* is referred to as a Medicinal Cannabis licence)

Other than in its dried form, a narcotic manufacture licence is not required where the cultivated and trimmed cannabis has not been through a solvent based extraction step. Note that this exemption does not negate the need for cultivation licence under the *Narcotic Drug Act 1967* to cultivate cannabis.

Administration and verification requirements

For medicinal cannabis with Schedule 8 ingredients (controlled substances) in the Poisons Standard, there are both administration and verification manufacturing requirements.

Administration requirements

The Schedule 8 status of some medicinal cannabis puts specific requirements on adequate administration of quantities of cannabis-containing materials that you:

- receive
- sample
- hold in storage at any particular point in time
- use
- supply (split up in recipients and shipments)
- discard
- destroy

These requirements apply throughout all manufacturing processes, including all handling.

The PIC/S Guide to GMP also includes requirements on recording quantities of materials and the reconciliation of these at the end of manufacture.

When manufacturing medicinal cannabis products, you can use one set of records and documentation that serves both purposes as long as these records comply with the GMP requirements as well as the requirements from the product's Scheduling.

Verification requirements

The Schedule 8 status of some medicinal cannabis also requires the manufacturer of medicinal cannabis products to verify that:

- each supplier of medicinal cannabis holds current licence(s) and permit(s) under the Narcotic Drugs Act that allow the supply of each delivery
- each of the customers to which you supply medicinal cannabis hold current licence(s) and permit(s) under the Narcotic Drugs Act that allow them to receive the delivery from you

Both verifications are required for **each delivery** and for **each supplier or customer**. The recommended way to meet these requirements is to include verification of:

- your supplier's licence to manufacture narcotic drugs in the supplier qualification process that is required under GMP
- the current status of that licence and the availability of the required narcotic drugs permits in your procedures on incoming goods receipt
- your customer's licence to manufacture narcotic drugs in your regular process to include customers in the customer database
- the current status of that licence and the availability of the required narcotic drugs permits in your procedures on outgoing goods shipment.

Import requirements

Where a product is imported, it must meet the TGA GMP requirements as well as the ODC requirements, unless exempt.

ODC requirements

Medicinal cannabis and medicinal cannabis products are regulated for import under the *Customs (Prohibited Export) Regulations 1956*.

These regulations are administered by ODC, more information can be found on the ODC import and export page.

TGA requirements

Information on TGA requirements regarding import can be found on the TGA website:

- Importing unapproved therapeutic goods and controlled substances

Importing considerations

Imported unapproved medicinal cannabis products for use through one of the access pathways schemes like SAS require an import licence and permit from the ODC.

Overseas manufacturers can obtain GMP certification following a successful on-site inspection by the TGA or via the compliance verification pathway, if applicable. See GMP clearance and certification for overseas manufacturers.

Declaration of intent to supply is requested as part of the process for certification of overseas manufacturers at the application review stage as per the Australian manufacturing licences and overseas GMP certification guidance.

PIC/S Guide to GMP

The PIC/S Guide to GMP, as determined in the latest therapeutic goods (manufacturing principles) determination, is the **mandatory standard** for the manufacture of medicinal cannabis under provisions of section 36 in the *Therapeutic Goods Act 1989*.

Section 36(1) of the *Therapeutic Goods Act 1989*: The Minister may, from time to time, determine written principles to be observed in the manufacture of therapeutic goods for use in humans.

The TGA uses internationally harmonised manufacturing standards, such as the PIC/S Guide to GMP to allow manufacturers to operate in an international environment.

The TGA adopted the PIC/S Guide to GMP, excluding Annexes 4, 5 and 14, as the manufacturing principles for:

- medicines and active pharmaceutical ingredients
- biologicals that comprise or contain live animal cells, tissues or organs

Periodic changes

GMP requirements change over time due to various reasons, such as to:

- provide guidance for the management of new technologies
- address gaps or clarify existing compliance requirements
- manage risks identified through inspections and regulation
- facilitate continuous improvements in the way medicines are manufactured

The TGA maintains its GMP standards in line with updates issued through PIC/S Guide to GMP. Regular updates are necessary to:

- maintain mutual confidence with international regulators
- promote quality assurance of inspections
- promote harmonisation of technical standards and procedures with international inspection standards for the production and testing of medicinal products

Application of the PIC/S Guide to GMP

The sections of the PIC/S Guide to GMP that apply to medicinal cannabis will be determined by the nature of your operations and the variety of products or dosage forms you manufacture.

For example, manufacturers of **finished dosage forms** should in general follow the principles of Part I of the PIC/S Guide to GMP. This includes all annexes relevant to their operations and dosage forms such as:

- Annex 7 (herbal products)
- Annex 8 (sampling)
- Annex 11 (computerised systems)
- Annex 15 (qualification and validation)
- Annex 19 (reference and retention samples)

Manufacturers of **active pharmaceutical ingredients** (APIs) should follow the principles of Part II of the Guide, including all annexes relevant to their operations, such as:

- Annex 7 (herbal products)
- Annex 19 (reference and retention samples)

Note that annexes 8, 11 and 15 do not directly apply to the manufacture of APIs for medicinal cannabis as specific guidance for APIs is provided within Part II of the guide; these annexes may be used as supplementary guidance without introducing additional requirements.

Guidance within annexes for specific dosage forms or product types should be read in conjunction with the relevant part of the Guide (Part I or II), e.g.:

- a manufacturer of medicinal cannabis dosage form made from herbal material i.e. non sterile Schedule 8 registered product should meet the requirements of Part I and Annexes 7, 8, 9, 11, 15 and 19
- a manufacturer of API herbal ingredient (medicinal cannabis API) and non sterile schedule 8 registered finished product should potentially meet both Part I & II with Annexes 7, 8, 11, 15 and 19

Further technical GMP guidance

The PIC/S Guide to GMP applies unless not applicable or replaced by alternatives based on quality risk management principles and the principles under Annex 13 (for manufacture of investigational medicinal products) and demonstrated to be effective.

These technical guidance documents have been originally developed for complementary medicines, they contain relevant guidance however, on risk management in manufacture, subject to the principles of Annex 20 of the PIC/S Guide to GMP.

- Supplier qualification
- Sampling and testing
- Process validation
- Product Quality Review
- Ongoing stability testing

Once medicinal cannabis products are registered in the ARTG, access pathways will no longer apply and therefore these technical guidance documents may no longer be relevant.

Terminology in the PIC/S Guide to GMP

Finished medicinal cannabis product

The finished medicinal cannabis product is the dosage form in which the medicinal cannabis is intended to be administered to the patient, for example as an oil, tincture, extract, capsule, tablet etc.

The manufacture of the finished medicinal cannabis product is required to be in compliance with Part I of the PIC/S Guide to GMP, as well as the relevant parts of the Annexes to the Guide.

Investigational medicines

Unapproved therapeutic goods not included on the ARTG and accessed through clinical trial schemes are referred to as 'investigational medicinal products' in the PIC/S Guide to GMP.

Quality management (Chapter 1, Part I - finished dosage form)

Terminology for quality management

Pharmaceutical quality system (PQS)

In the latest PIC/S Guide to GMP, the terminology 'Quality Management System' has been replaced with the term 'Pharmaceutical Quality System' (PQS). This is in line with ICH Q10 global harmonisation efforts, PIC/S harmonisation efforts and to align the PIC/S Guide to GMP with contemporary principles of quality systems management.

The new terminology better reflects the specific design elements and requirements for a quality system used to manage the manufacture of medicinal products. The PQS approach described within the PIC/S Guide to GMP is applicable to the manufacture of all therapeutic goods to which the PIC/S Guide to GMP applies.

Manufacturing authorisation

The term manufacturing authorisation refers to either the licence to manufacture therapeutic goods (GMP) to Australian manufacturers or, for manufacturers located overseas, this refers to the certificate of GMP compliance issued following an inspection. These are licences, clearances and certifications issued by the TGA.

Marketing authorisation

A marketing authorisation (MA) is the approval given to supply a therapeutic good in Australia, and involves entry in the Australian Register of Therapeutic Goods (ARTG).

The marketing authorisation includes the details of the product in the ARTG, as well as all other matters in relation to product registration, listing or inclusion agreed in writing between the TGA and the sponsor, and any other requirements imposed by a relevant Delegate of the Secretary upon ARTG entry.

Examples of regulatory requirements include, but are not limited to:

- compliance with standards and registered formulations
- special storage and transportation conditions
- shelf life
- packaging and labelling
- batch release testing requirements

Manufacturers are responsible for ensuring their PQS is designed and operated to ensure all relevant requirements of the marketing authorisation are observed during the manufacture of medicines.

Holder of the marketing authorisation

The holder of the marketing authorisation is the product sponsor.

Change management

Changes in manufacture are regulated

Manufacturing changes that affect the product's registered details on the ARTG are regulated by TGA. To understand your obligations when changing aspects of manufacturing on the ARTG entry for the goods, please consult the Australian Regulatory Guidelines for Prescription Medicines (ARGPM).

These requirements are mandatory and are in addition to the requirements of the PIC/S Guide to GMP.

The requirements within the PIC/S Guide to GMP in relation to change control and risk assessment apply to all changes in manufacture, including those not captured in the ARGPM.

Change control applies to all GMP-related activities

Change control is included in Chapter 1 of the PIC/S Guide to GMP (Clause 1.4 xii, xiii). This clarifies the existing expectation that change control does not just apply to validation activities, but to all GMP-related activities undertaken by a manufacturer.

Any changes to existing processes, systems, facilities, equipment, products, documents, and others should be evaluated through a change control process. The effort and extent of change control processes should be commensurate with the nature of the change and based on risk management principles.

All changes implemented should be verified for their effectiveness following implementation.

Managing deviations

The PIC/S Guide to GMP provides clarity regarding the expectations for the investigation of deviations, including adequate root-cause-analysis and identification of corrective and preventative actions (clause 1.4 xiv).

Release for supply (RFS)

For more information on release for supply (RFS), refer to:

- TGA guidance on Release for supply of medicines

Sponsor performing RFS

Release for supply is defined as a manufacturing step for which a TGA licence is required. For this reason, a sponsor can only perform batch certification for the purposes of release for supply (clause 1.4xv) if:

- the sponsor holds a TGA licence to manufacture therapeutic goods (GMP)

and

- the licensed sponsor is authorised within the marketing authorisation for that step in manufacture

Having more than one authorised person for RFS

A manufacturer is allowed to have more than one authorised person to perform release for supply. It is the manufacturer's responsibility to ensure that each authorised person is appropriately trained and experienced and that the job function relating to release is clearly documented and explained in the PQS.

Authorised person needs full overview of all manufacturing steps

The authorised person responsible for release for supply should have a full overview of all manufacturing steps, including those performed by other manufacturers.

Consequently, the last manufacturer in the supply chain for each batch of product is normally responsible for release for supply. However, the authorised person may be identified from any of the manufacturers authorised for release for supply in the marketing authorisation, as long as they have full overview of all steps performed in the manufacture of the batch involved and have full access to all details of the marketing authorisation.

RFS includes consideration of marketing authorisation requirements

The TGA expects an authorised person to carry out release for supply to ensure the products meet all regulatory requirements.

Release for supply must include assurance of compliance with the marketing authorisation, as well as meeting all relevant GMP requirements, including assessing Product Quality Reviews (PQRs) and the effectiveness of the on-going stability program. This applies to inspections of both Australian and overseas manufacturers.

Senior management responsibilities for GMP and quality management

Clauses in the PIC/S Guide to GMP (including clause 1.5) place particular emphasis on the roles and responsibilities of senior management who have ultimate control over manufacturing facilities and activities.

Senior management hold the responsibility to make sure that adequate resources are available (human, financial and physical) in order to ensure that the manufacturing activity is managed appropriately.

It is expected that senior management ensure that an effective PQS is implemented and undertake an active role in the support, development and implementation of the PQS. Senior management are ultimately responsible and accountable for the effectiveness of the PQS.

Management reviews

Management reviews (clause 1.6) are a basic quality system element designed to collate, evaluate and communicate details of the effectiveness of the PQS to the management group. Management reviews are particularly important in escalating concerns and enabling senior management support with the aim of resolving issues and managing risks.

The TGA's expectations, based on ICH Q10 principles are that the management review system should include:

- the results of regulatory inspections and findings, audits and other assessments, and commitments made to regulatory authorities

- periodic quality reviews, that can include:
  - measures of customer satisfaction such as product quality complaints and recalls
  - conclusions of process performance and product quality monitoring
  - the effectiveness of process and product changes including those arising from corrective action and preventive actions
- any follow-up actions from previous management reviews

The management review system should identify appropriate actions, such as:

- improvements to manufacturing processes and products
- provision, training and/or realignment of resources
- capture and dissemination of knowledge

Management review of the PQS

Management should have a formal process for reviewing the PQS on a periodic basis. The review should include:

- measurement of achievement of PQS objectives
- assessment of performance indicators that can be used to monitor the effectiveness of processes within the pharmaceutical quality system, such as:
  - complaint, deviation, corrective and preventative actions (CAPA) and change management processes
  - feedback on outsourced activities
  - self-assessment processes including risk assessments, trending, and audits
  - external assessments such as regulatory inspections and findings and customer audits

Monitoring of internal and external factors impacting the PQS monitored by management can include:

- emerging regulations, guidance and quality issues that can impact the PQS
- innovations that might enhance the PQS
- changes in business environment and objectives
- changes in product ownership

Frequency of management reviews

TGA inspectors would generally expect reviews to be conducted at least annually (clause 1.6). However, management reviews may be performed more frequently for sites:

- with new operations
- that have not previously performed management reviews
- where the initial management review identifies a number of issues that require rectification
- with larger and more diverse manufacturing operations

Development of a quality manual

Clause 1.7 in the PIC/S Guide to GMP requires a quality manual (or equivalent document) to be written and maintained.

A quality manual or equivalent should be established and should contain the description of the PQS. The description should include:

- the quality policy
- the scope of the PQS
- identification of the PQS processes, as well as their sequences, linkages and interdependencies. Process maps and flow charts can be useful tools to facilitate depicting PQS processes in a visual manner
- management responsibilities within the PQS

Product distribution expectations

Clause 1.8 (ix) states that the distribution of the products minimises any risk to their quality and takes account of 'good distribution practice'.

The TGA does not currently inspect the wholesale distribution of therapeutic goods that have been released for supply.

The responsibility for oversight of wholesale of medicines in schedules 2, 3, 4 & 8 of the Poisons Standard currently sits with the states and territories, who may issue relevant permits and licences for wholesalers.

When TGA inspections include an evaluation of the transport conditions for starting materials and bulk and packed medicines between sites of manufacture then clause 1.8 (ix) would apply in these circumstances.

Good Distribution Practices (GDP) in the case of Australia would be limited to the application of transport requirements specified in Annex 15 of the PIC/S Guide to GMP and not necessarily any other official GDP guideline.

Product quality reviews (PQRs)

Further guidance regarding the documentation requirements for PQRs can be found in the TGA guidance on Release for supply of medicines.

PQRs for authorised products

'All authorised products' in clause 1.10 refers to all products manufactured, within the reviewed time period, under a manufacturing authorisation. This implies that Australian manufacturers are expected to conduct PQRs for **all** medicinal products manufactured under the manufacturing licence and overseas manufacturers are expected to conduct PQRs for **all** medicinal products for which a GMP clearance is granted.

PQRs for products with no marketing authorisation

PQRs are performed to demonstrate the consistency of the manufacturing process. Where no marketing authorisation is applicable/available, clauses 1.10.vi and 1.10.x do not apply, but a review of the process consistency, including all other elements of clause 1.10 should be performed and documented by the manufacturer. Principles in Annex 13 would also need to be considered.

Supply chain traceability for active substances

Manufacturers of dosage forms should have a clear understanding of the approved suppliers of active substances, and their responsibilities in the supply chain between the site of manufacture and receipt (clause 1.10(i)).

Supply chains should be adequately secure, integral and ensure that materials are transported under appropriate conditions. Supply chains should be mapped and any identified risks managed following the principles of quality risk management.

Guidance for the evaluation of supply chains for active ingredients used in non-sterile medicinal cannabis products may be found in our guidance about Supplier assessment, approval and qualification.

Frequency of PQRs

It is important that manufacturers perform a review of all relevant elements of clause 1.10 on at least a yearly basis; however, where very few batches of one product are manufactured in one year, or no manufacturing takes place, it may also be acceptable to perform a full PQR on a two yearly basis providing a rationale is documented and scientifically justified.

For periods where very few batches of one product are manufactured in one year, or no manufacturing takes place, it is expected that manufacturers and sponsors maintain vigilance over elements of clause 1.10 that do not directly relate to manufacturing activities, e.g. results of ongoing stability, returns, recalls and complaints that may provide information regarding products available in the market.

Grouping of products for PQRs

Grouping (sometimes referred to as bracketing or matrixing) of products is when one PQR is prepared for a group of products. Grouping for the preparation of PQRs may be acceptable, if adequately justified. It is usually only acceptable if:

- the amount of batches manufactured annually for each product within the group is low
- the grouped products are of the same pharmaceutical form containing the same or very similar active ingredients and are manufactured using the same equipment

Acceptability of grouping will be assessed during inspections on a case-by-case basis, and with consideration to any applicable GMP guidance.

Batches to be included in a PQR

All batches for which manufacture has commenced are expected to be included in a PQR. In addition, all batches for which the manufacture was terminated, delayed or has failed are also expected to be included in the PQRs. When grouping is applied, all batches of all products in each group are expected to be included in the PQR.

Shared responsibility for PQRs between manufacturers and the sponsor

Preparation of PQRs is a shared responsibility between the sponsor and the manufacturer(s) of a product. Manufacturers and sponsors should design and implement effective systems to ensure that PQR reports and relevant data are supplied, compiled and reviewed. Responsibilities in relation to PQRs should be clearly defined within technical agreements between parties.

Each manufacturer in the supply chain is expected to generate and hold PQRs relevant to the specific manufacturing step they are undertaking. These are expected to be supplied to the sponsor and available for review during inspections of manufacturers.

The full PQR containing all relevant sections from all manufacturers should be held and reviewed by authorised persons performing the release for supply step. Sponsors are also expected to have access to the PQRs, to ensure product compliance with the marketing authorisation.

Quality risk management

Quality risk management is mandatory

Clauses 1.12 and 1.13 of Part I (also and clauses 2.20 and 2.21 of Part II) of the PIC/S Guide to GMP make it a mandatory requirement for manufacturers to have an operational quality risk management system in place to ensure that the evaluation of a risk to product quality is based on a sound, scientific basis and that risk assessments are appropriately documented.

Annex 20 is voluntary and provides guidance only on quality risk management tools that may be applied by a manufacturer when assessing the risk to product quality.

Personnel (Chapter 2, Part I - finished dosage form)

Senior management responsibilities for personnel

New clauses in the PIC/S Guide to GMP (including clause 2.1) place particular emphasis on the roles and responsibilities of senior management who have ultimate control over manufacturing facilities and activities. Senior management are accountable for ensuring appropriate resources are available to support the relevant manufacturing activities.

Personnel qualifications

Necessary qualifications for staff

'Necessary qualifications' in clause 2.1 means having the education, training, experience and skills, or any combination of these elements, that will ensure that staff can perform assigned duties and functions at an acceptable level.

Qualification requirements for an Authorised Person

There are no minimum qualification requirements for Authorised Persons specified within Australian legislation. However, in accordance with GMP, senior management should ensure that person(s) undertaking the role of Authorised Person have the education, training, experience and skills or any combination of these elements to ensure that they can perform the role of the Authorised Person.

In general, an authorised person should be able to demonstrate the following competencies:

- knowledge of the requirements of GMP applicable to the dosage forms for which they are responsible
- a comprehensive understanding of the manufacturing methods and controls for the specific dosage form(s) for which they are responsible
- knowledge of the regulatory requirements relevant to the dosage forms manufactured by their site. In particular, knowledge of the marketing authorisation requirements for the specific products for which they are responsible
- working knowledge of the PQS implemented at their manufacturing site

Expectations for training and language

Training requirements

Training and assessment should be carried out by persons with relevant training, qualifications and experience in the subject matter (clauses 2.10 to 2.14).

Training should be given to all people affected by significant change in the PQS, e.g. when SOPs or methods of manufacture change. The requirement for initial and ongoing training should be reflected in procedures, and training records should be generated and kept.

There are a number of people who have a direct bearing on quality outcomes. These include senior management, contractors, consultants and casual employees. Therefore, appropriate training and assessment should be provided and recorded.

Language requirements

Manufacturers should define language requirements or standards and ensure personnel are proficient in the required language for their allocated tasks, particularly in relation to documenting and recording. Procedures employed to overcome identifiable deficiencies should also be documented.

Role of consultants

Management of consultants

Where consultants are engaged by a manufacturer to assist in operations, it is important that adequate records are kept and maintained, these include:

- contracts between the manufacturer and consultant outlining the scope of services
- up-to-date copies of each consultant's curriculum vitae
- job descriptions outlining roles, responsibilities, delegations and/or authorisations
- training records for local PQS procedures relevant to their role

It is the responsibility of the manufacturer to assess consultants and to ensure that they have adequate education, training, and experience, or any combination thereof, relevant to the services for which they are engaged.

Approval of controlled documents

Consultants are permitted (where defined by agreements) to write, review and approve documents within the PQS; however, the licence holder ultimately remains responsible for the content of, and adherence to authorised procedures within their PQS and cannot delegate or discharge the overall responsibility for the accuracy and content of documents signed by the consultants.

Premises and equipment (Chapter 3, Part I - finished dosage form)

Environmental controls

Environment for sampling non-sterile starting materials

Clause 3.9 describes the physical requirements for the area being used to sample non-sterile starting materials.

In order to protect the sampled material from contamination, this sampling would be expected to be carried out in a separate room, or appropriately qualified sampling hood, that supplies air of a quality and cleanliness equivalent to that used in the manufacturing area where the material is exposed. The sampling area would also be expected to be designed with dust extraction or equivalent controls to prevent contamination of adjacent areas.

Areas for the sampling of starting materials used in non-sterile products should be filtered using air filters of at least EU7 grade or equivalent. Areas used for the sampling of non-sterile starting materials used in the manufacture of sterile products should be designed and controlled in accordance with Annex 1 requirements.

Sampling hoods may be used provided there are adequate controls in place to ensure that materials are contained. Consideration should be given to the use of appropriate extraction/de-dusting facilities, the qualification of the hood, the possibility of contaminating the sampled material and adjacent storage area and whether materials sampled are hazardous.

Sampling primary packaging materials for non-sterile products

Clause 3.9 also describes the physical requirements for the area being used to sample primary packaging material for non-sterile products. As product-contact components, primary packaging materials should be sampled within an environment that adequately protects the packaging from contamination. However, sampling of primary packaging materials in an open warehouse would not be allowed.

Air quality for non-sterile medicine manufacture

The PIC/S Guide to GMP does not reference a specific standard for air quality for non-sterile manufacturing areas. There are also no Australian or ISO standards for air quality specific to non-sterile medicine manufacture.

In all cases, it is the manufacturer's responsibility to ensure that thorough qualification, validation and monitoring processes are in place to justify heating, ventilation and air-conditioning (HVAC) design and demonstrate that the air quality is sufficient for non-sterile manufacturing areas.

Manufacturers are required to demonstrate that the manufacturing environment for non-sterile products affords appropriate protection to the products, and prevents contamination. Use a risk-based approach to determine the required air quality and associated controls, based on a thorough understanding of:

- the manufacturing processes
- the nature of the product handled
- risks of contamination and cross-contamination
- risks to product quality

Minimum expectations

As a minimum expectation:

- air quality requirements (physical and microbiological) should be defined during system design and compliance demonstrated through qualification and on-going monitoring
- air filters used in manufacturing areas where product is exposed should be at least EU7 grade or equivalent
  - higher efficiency air filters may be required for products or processes that present a contamination risk
- pressure differentials and air flows must be defined and appropriate

Additional guidance

For additional guidance in relation to recommended levels of air filtration:

- World Health Organization: Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms

Cleaning and sanitisation

The PIC/S Guide to GMP contains limited detail on requirements for cleaning and sanitisation. This is because the manufacturer is responsible for demonstrating that the applied cleaning and sanitisation procedures are suitable for its intended purpose. This can be demonstrated by qualification, validation and monitoring studies. The extent of these studies will depend on the nature and types of products manufactured and the associated risks of contamination.

Premises and equipment definitions

Campaign manufacture

Clause 5.19 defines campaign manufacture as being a separation in time of production. That is, manufacturing a series of batches of the same product in sequence in a given period of time and/or maximum number of batches followed by an appropriate (validated) cleaning procedure.

Campaign manufacturing operations may be performed where the manufacturer has undertaken an appropriate risk assessment of the proposed operations, considering all potential risks to product quality, and detailed instructions regarding the management of operations and associated control measures are in place.

Clause 3.6 – meaning of ‘certain’

In clause 3.6 of the PIC/S Guide to GMP, the word 'certain' (as per certain additional products, certain antibiotics, certain hormones etc.) refers to materials known to cause specific (side) effects in low doses. For example:

- 'certain antibiotics' refers to antibiotics, usually of the beta lactam group, which are known to cause allergic reactions
- 'certain hormones' refers to hormones that can have pharmacological effects if trace amounts cross-contaminate other products e.g. oestrogens and some progesterone-like hormones

Manufacturers should evaluate materials that are processed and ensure that adequate control measures are in place.

Dedicated equipment may be required for potentially allergenic or sensitising products.

Dedicated facilities are normally required where the risk associated with the material cannot be adequately controlled by operational and technical measures, or the available scientific toxicological data does not support a controllable risk.

With respect to manufacture of medicinal cannabis products, dedicated premise/equipment would be preferable to ensure security and control of the operation. However, where adequate risk control is implemented and that all related operational and technical means are scientifically justified then non dedication may be acceptable.

Further guidance may be found in:

- EMA/CHMP/CVMP/SWP/246844/2018- Questions and answers on implementation of risk based prevention of cross contamination in production

Warehouses and distribution centres

By definition, 'manufacture' includes all steps in bringing the product to its final form and 'release for supply' is considered to be the last step in this process.

From a GMP point of view, warehousing and distribution after release for supply and after the product has left the manufacturer's control, is not currently regulated by the TGA. Hence, a facility that is used only for warehousing and distribution of **fully finished and released** products does not require a TGA manufacturing licence and is not required to comply with the PIC/S guide to GMP for medicinal products.

However, for an effective recall, cooperation from wholesalers and distributors is often essential. As a wholesaler, you should have a procedure for conducting a recall at a sponsor's request. For more information, refer to:

- Uniform recall procedure for therapeutic goods

There may be state or territory regulatory requirements that are applicable, which should be checked with the relevant state or territory authority.

Documentation (Chapter 4, Part I - finished dosage form)

Specifications

The TGA will not evaluate the raw material and finished product specifications for unapproved medicinal cannabis products to ensure these comply with the Therapeutic Goods (Standard for Medicinal Cannabis) (TGO 93) Order.

The manufacturer is required to review their raw material and finished product specifications against the requirements of TGO 93. If you are satisfied that your unapproved medicinal cannabis product(s) meet the requirements of the standard, you should complete the declaration form available on the TGA website to declare that your medicinal cannabis product(s) meets this standard. The TGA may ask for a representative certificate of analysis for review to ensure compliance with TGO93. Medicinal cannabis products, like all therapeutic goods may be subject to testing by the TGA to confirm compliance with applicable standards.

GMP inspectors will review the specifications and certificates of analysis as part of the GMP inspection to confirm you are meeting appropriate standards.

Retention of batch documents

Batch documents must be kept for at least one year after the expiry date or at least 5 years after release for supply by the authorised person, whichever is the longest. The batch documentation for investigational products must be kept for at least 5 years following completion or formal discontinuation of the last clinical trial. Other times of retention of batch documents may be required based on specific legislative requirements.

Authorised person access to records

As the Authorised Person for release for supply takes responsibility for releasing and placing batches of product on the market, it is important that they have appropriate access to any documents that facilitate or influence their decisions. Accordingly, systems should be implemented to facilitate an authorised person's access to all documentation relevant to a specific batch, including, but not limited to, validation documents, stability data, test results and batch records.

Guidance as to the minimum documentation required to be held by authorised persons performing release for supply of products manufactured under contract may be found in the TGA guidance on Release for supply of medicines.

Batch numbers in distribution records

Distribution records require batch numbers (clause 4.28). According to clause 8.13 the recording of batch numbers in distribution records is mandatory.

Signature list

Manufacturers need to maintain a signature list. These should include the names, signatures and initials used by individuals who complete GMP documentation. The signature list is the key reference when providing traceability between manual signatures used on documents and the individuals who completed them.

Production (Chapter 5, Part I - finished dosage form)

Medicine production

The requirements of the PIC/S Guide to GMP apply, unless the specific requirements are not applicable to the specific manufacturing activity, or equivalent level of compliance is achieved by alternative means. Any omission or alternative approach to compliance must be based on quality risk management principles. Where products are made for use in clinical trials the principles under Annex 13 should be considered.

Refer to the technical GMP guidance documents, developed for the application of quality risk management in the manufacture of complementary medicines, noted previously. These documents contain information that may assist you in the application of quality risk management for the manufacture of unapproved medicinal cannabis products to be made available via clinical trials or the other access pathways.

Once medicinal cannabis products are registered in the ARTG, access pathways will no longer apply and therefore these technical guidance documents may no longer be relevant.

Labelling and packaging

Label counting and verification

Roll labels must be counted either on receipt or at issue. Supplier counts are not acceptable unless the supplier is specifically qualified and the supplier certifies the exact count for each roll. Supplier sequential numbering on the backing web of labels is an acceptable alternative.

Cut labels must be counted and effectively verified by the manufacturer because of risks of mix-ups.

Unique batch numbering

The system that a manufacturer adopts for batch numbering may include numerals, letters or symbols (or any combination of these) and must effectively serve to identify uniquely a batch of product, and from which it is possible to trace that batch through all stages of manufacture and distribution. The manufacturer should be able to demonstrate that the system for batch numbering meets these requirements and is effective.

Unpacked bulk products, should have a batch number that is unique to both product and batch, to minimise the potential for mix-ups during manufacturing. For finished products which are easily distinguished, a batch numbering system that only designates batches from that product may be acceptable.

The topic of batch numbering is dealt with in:

- Medicines labels: Guidance on TGO 91 and 92

Quality control (Chapter 6, Part I - finished dosage form)

Testing

In addition to the requirements outlined in the PIC/S guide to GMP, there are various standards that apply to medicinal cannabis products, including but not limited to, the Therapeutic Goods (Standard for Medicinal Cannabis) (TGO 93) Order.

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 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. The manufacturer should ensure that the product will meet all the requirements of the standard.

Conducting on-going stability studies

Principles for conducting on-going stability studies

In general, on-going stability studies should be based on the principles of ICH Q1.

Ongoing stability would not normally be applicable for clinical trial material. Stability would be required according to Annex 13 to support the expiry date for the material. The clauses that would be applicable for stability of clinical trial material include Annex 13, clauses 6, 9, 20, 26j and 40.

Use of on-going stability program results in release for supply

The results of the on-going stability program are expected to be available to the authorised person who should consider the results before releasing a batch for supply.

On-going stability studies in a GMP certified laboratory

Ongoing stability testing does not need to be conducted in a GMP certified laboratory, because ongoing stability testing is not considered to be a step in manufacture, as defined by the *Therapeutic Goods Act 1989*.

However, the results from these studies are required to be reliable and meaningful. It is the responsibility of the contract giver (typically a manufacturer or sponsor) to ensure that any laboratories used for ongoing stability testing is appropriate.

For that reason, other certification may be used in lieu of a GMP certification, such as a licence issued by a regulatory authority acceptable to the TGA or a current ISO 17025 accreditation. Stability test methods used by the laboratory should be appropriately validated and documented according to the requirements of the PIC/S Guide to GMP.

The results from the on-going stability monitoring studies must be considered as part of release for supply, which is the final step in manufacturing.

Responsibility for ongoing stability studies of imported medicines

In the case of imported medicines, the responsibility to conduct an on-going stability monitoring program is with both the manufacturer and the sponsor:

- The manufacturer who carries out release for supply needs to ensure that the batch meets its marketing authorisation, and that an on-going stability monitoring program is conducted and data is available to support the expiry date.
- The sponsor is responsible for the marketing authorisation and ensures an on-going stability testing program is performed and has access to the stability results.

In the contract manufacturing agreement, the responsibility for on-going stability may be contracted out to the manufacturer or other parties.

Bulk medicine on-going stability studies

Where bulk medicines are imported into Australia to be packaged by an Australian manufacturer, the Australian manufacturer cannot use the on-going stability program of the bulk manufacturer to support the packed product stability.

On-going stability is required to be performed in the packaging material in which the product is marketed in Australia. The overseas bulk manufacturer will use different packaging equipment and processes although the packaging materials might be the same.

Grouping for the purposes of stability testing

Grouping (also known as bracketing or matrixing) could be acceptable, if scientifically justified. This will be assessed during inspections on a case-by-case basis. This is applicable to medicinal cannabis products provided the active cannabinoid type is considered in the grouping.

Review of on-going stability data during inspections

During inspections, the operation of an appropriate on-going stability program is normally reviewed, including the results of on-going stability studies, where appropriate. If there are any concerns, the inspector can refer the evaluation to the area of the TGA responsible for regulating the product ARTG entry.

Notifying TGA of on-going stability issues

Although it is acknowledged that some normal variability in the results of on-going stability studies can be expected, all statistically significant departures from established stability profiles must be notified to the area of the TGA responsible for regulating the product ARTG entry. In general, 'significant change' for a medicinal product is defined as:

- a 5% change in assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedures
- any degradation products exceeding its acceptance criterion
- failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g. colour, phase separation, re-suspendibility, caking, hardness, dose delivery per actuation); however, some changes in physical attributes (e.g. softening of suppositories, melting of creams) may be expected under accelerated conditions

or

- as appropriate for the dosage form:
  - failure to meet the acceptance criterion for pH

  or

  - failure to meet the acceptance criteria for dissolution for 12 dosage units

Outsourced activities (Chapter 7, Part I - finished dosage form)

Change in scope of chapter 7

The title of chapter 7 has changed from 'Contract manufacturer and analysis' to 'Outsourced activities' in recognition of the fact that there are a number of outsourced (contracted) activities that may have a direct effect on the quality of medicinal product manufactured by a site.

The previous title of the chapter restricted the extent of GMP controls to only outsourced manufacturing and testing services and thus did not appropriately manage the risk associated with other outsourced activities.

Examples of outsourced activities that this chapter would now include, but are not limited to:

- contract manufacturing and analysis
- maintenance and calibration services
- providers of critical consumables, e.g. gowns, sterilised componentry
- suppliers and manufacturers of raw materials, packaging materials and printed artwork
- provision of training and consulting services
- validation services associated with facilities, equipment, utilities, process and product design, qualification and validation
- provision of transport and logistical services for products
- contract cleaning and waste management services
- contract pest control services
- agencies that provide temporary or contract personnel

Managing outsourced activities

The TGA expects manufacturers (normally 'contract givers') to manage all relationships with contract acceptors in accordance with existing principles of chapter 7. All outsourced GMP-related activities that may impact on product quality should be assessed, defined and covered by a written contract. Agreements should be maintained in accordance with the PQS.

Legality of outsourced activities

The term 'legality' in clause 7.4.1 means that contract givers are responsible for making sure that the entity undertaking the outsourced activities is appropriately authorised to undertake the activity. This may be achieved by many means including ensuring that the contract acceptor:

- holds the appropriate manufacturing authorisation (licence) to undertake the specific steps in manufacture
- is nominated as being authorised to undertake the specific activity in the specific marketing authorisation of the products

- holds any necessary licenses or permits applicable to the outsourced activities, e.g. wholesale authorisations, Schedule 8 drugs permits etc.
- holds the necessary accreditation related to the activities undertaken, e.g. a contract calibration company may hold National Association of Testing Authorities (NATA) or ISO 17025 certification

Monitoring the contract acceptor

The contract giver should have a system in place to measure and monitor the quality of products (or service) provided by the contract acceptor, in accordance with risk management principles.

Where quality related issues are identified, it is expected that appropriate actions are taken to address and remediate the concerns. Records of actions taken should be recorded within the PQS.

Responsibility for review of records and results

Clause 7.5 states that the contract giver should be responsible for reviewing and assessing the records and the results related to the outsourced activities.

It is expected that the responsibility for review of the records and results to be specified by contract and should be based on the risk and nature of the service provided e.g.:

- For contract manufacture and analyses, it may be appropriate for the contract giver to rely fully on the contract acceptor where an authorised representative of the contract acceptor, e.g. quality manager, has authorised the data and records.
- For contract service providers (e.g. contract calibration services) it would be appropriate for the contract giver to review the available records and data to ensure that the results or work provided meet the requirements of the contract giver's quality system and procedures.

Complaints and product recall (Chapter 8, Part I - finished dosage form)

Counterfeit products

Clauses 8.7 and 8.8 of the PIC/S Guide to GMP require that the procedures on complaints handling should include an assessment for counterfeit products. If counterfeiting is detected the TGA must be notified in accordance with the Uniform Recall Procedure for Therapeutic Goods (URPTG).

Annexes of the PIC/S Guide to GMP

The Annexes to the code of GMP apply to Parts I and II, i.e. to the manufacture of cannabis as an active pharmaceutical ingredient as well as to the manufacture of the finished medicinal cannabis product.

All GMP Annexes that are relevant to your manufacturing processes apply. This may depend on the dosage form manufactured, or on specific process characteristics.

GMP Annexes that are relevant to the manufacture of **all non-sterile medicinal cannabis products** are:

- Annex 7 - Manufacture of herbal medicinal products
- Annex 8 - Sampling of starting and packaging materials
- Annex 15 – Qualification and validation
- Annex 19 – Reference and retention samples
- Annex 20 – Quality risk management

Please note

Annex 20 is not mandatory; it is a tool to assist you in satisfying the mandatory clauses 1.5 and 1.6 in Part I of the Code of GMP.

Annexes that may be relevant to the manufacture of medicinal cannabis products, depending on dosage form and process characteristics, are:

- Annex 9 – Manufacture of liquids, creams and ointments: only relevant for medicinal cannabis products in these dosage forms
- Annex 11 – Computerised systems: only relevant for manufacturing processes or testing activities, where computer systems are used
- Annex 13 – Manufacture of investigational medicinal products: only relevant for medicinal cannabis products for use in clinical trials

Herbal medicinal products (Annex 7)

Reference standards

If an active or marker compound is identified and no commercially available primary standard is available, a suitably controlled and characterised reference material of that compound should be obtained from external sources.

Quantified by input

Quantified by input (QBI) is applicable to listed complementary medicines only. Medicinal cannabis products, once registered on the ARTG will contain a restricted ingredient/component and therefore quantitative testing of the active ingredient in the finished product would be required.

QBI is also not applicable to unapproved medicinal cannabis product dosage forms made available under the access pathways.

Good agricultural and collection practices (GACP)

Statements within this Annex relating to Good Agricultural and Collection Practices (GACP) are not mandatory.

Alternative methods of assuring the suitability and quality of herbal starting materials are permissible. It is recommended that GACP are considered during supplier qualification, as GACP may assist in influencing routine sampling and testing programs for herbal starting materials.

Some other countries may seek to import material specifically compliant with GACP- it is a matter for the exporter to determine relevant country import requirements.

The recommendations regarding GACP apply to manufacturers involved in the cultivation of herbal starting materials (herbs) only.

The grower/supplier of the medicinal cannabis plant or the API substance manufacturer should provide a written GACP declaration and the supporting documentation to the manufacturer of the finished product. This will be assessed as part of supplier qualification.

Adulteration or substitution of herbal substances

Manufacturers should assess the range of herbal substances used in order to determine whether specific herbal substance is at risk of adulteration or substitution. Potential risk factors include:

- materials with high intrinsic value that may be substituted or ‘bulked-out’ with other materials, i.e. cheap plant material, fillers
- highly active compounds including Schedule 8 medicines
- ingredients that may be adulterated with medicinal substances included in schedules 3, 4 and 8 of the Poisons Standard, e.g. steroids, diuretics, stimulants or medicines used in the treatment of erectile dysfunction

- herbal materials that are difficult to distinguish microscopically, e.g. milled or powdered materials and plant parts that have very similar microscopic appearance
- materials from new sources especially in circumstances where the reputation of reliability of the supplier is not known
- large offers of herbal materials that are generally only available in limited quantities
- out-of-range prices for materials

The justification and application of additional testing should follow basic risk management principles.

Identification of herbal materials

The TGA has published guidance regarding the requirements for Identification of herbal materials and extracts.

Samples of unmilled plants

Manufacturers performing the identity testing of herbal materials are required to hold appropriate certified/authenticated reference samples for the herbal materials used.

Reference samples should be traceable back to a suitable primary reference material. Where powdered materials are used in the manufacture of an API or product, the manufacturer performing the testing is expected to hold an appropriate certified reference material of unmilled plant. This is due to the inherent difficulties and risks associated with the identification of powdered plants.

Sampling of starting and packaging material (Annex 8)

Reduced sampling of starting materials

It is improbable that reduced sampling and testing would be accepted for:

- starting materials supplied by intermediaries such as brokers where the source of manufacture is unknown or not audited
- starting materials for use in parenteral products

A validated procedure that would permit less than all containers to be sampled and tested for identification purposes should consider the following:

- every container of starting material must be sampled and tested for identity if the supplier is not classified as reliable and is not validated according to Annex 8
- for registered medicines, the requirements for sampling active materials do not differ from those for excipients
- the validation of a supplier cannot be accepted without a regular and adequate assessment. Such validation should comprise a number of actions, which may include all or most of the following:
  - the use of a questionnaire prepared by the potential customer and completed by the potential supplier, concerning the supplier's operating Quality System
  - approval inspection of the potential supplier's operation by the potential customer, or by a third party on their behalf. For example, a sister company located in the same country as the supplier. Reliance on inspection reports of other regulatory authorities by the potential customer is normally not sufficient, unless it can be demonstrated that the inspection covered the specific operations to be used in the processing of materials for the potential customer.
  - a program to evaluate the quality of each shipment of materials on receipt by the customer. In this regard, sampling of powders should be representative of the container contents. For example, sampling from the top, middle and bottom of drums, in the absence of validated sampling positions. Reduced testing programs should be evaluated by the customer and where sampling was conducted by the suppliers, it should be validated.
  - a program for regular re-inspection of the supplier's operation and for ongoing monitoring of the quality of material supplied, for example, through trend analysis of analytical results, periodic full testing
  - in the case of active ingredients, the use of brokers as sources should be carefully evaluated. The quality of each batch of material should be confirmed through testing of representative samples.

Certification such as a Certificate of Suitability for Compliance with Monographs of the European Pharmacopoeia, does not replace an inspection.

Application of reduced sampling

Where a validated procedure is established to justify reduced sampling, and scientific and statistical evidence is presented, a $\sqrt{n}+1$ or similar sampling plans may be justified.

Computerised systems (Annex 11)

Annex 11 has been updated to provide clarification of existing requirements to ensure that computerised systems are managed appropriately, particularly in relation to data management and integrity.

Validation and control of computerised systems

All computerised systems (including commercial off-the-shelf systems) used by licensed manufacturers in the manufacture of medicines should be validated and controlled in accordance with Annex 11 requirements (i.e. GMP computerised systems).

The level, extent and formality of system control should be commensurate with the criticality of the system. Manufacturers should have a good understanding of all the systems used, and the impact and criticality of each system.

In general, the following systems (list is not exhaustive) should be fully validated and controlled, such as those used:

- for the electronic acquisition of quality control data
- to control and monitor the operation of critical utilities, facilities and equipment
- to generate, store or access electronic GMP records
- to generate, process, calculate or monitor data that forms part of the batch processing record, or batch control testing records
- in the place of physical (hard-copy) records, e.g. electronic spreadsheets used to track records or perform calculations, electronic documents used to record data
- to control the status of materials, products, equipment or processes, e.g. Enterprise Resource Planning systems
- to perform the release of materials and release for supply of finished goods
- to track the distribution of products and/or control the reconciliation of products and materials in the case of quality defects or recalls
- to acquire and store environmental data such as temperature, humidity, and differential pressures
- to manage quality investigations and store and track investigation records. For example, deviations, out of specifications, complaints and change control

‘Regulated users’ definition

The TGA regards ‘regulated users’ to be the licence or GMP certificate holder responsible for the application of GMP.

‘Life-cycle’ of a computerised system

The ‘life-cycle’ of a computerised system includes all stages from the initial concept, design, qualification, validation, and use through to the eventual retirement of the system and archival of all data.

Manufacturers need to manage computerised systems effectively at all stages in the life-cycle to ensure that they function correctly. Therefore, validation not only applies at the initial introduction of the system, but throughout all stages of use. Further guidance regarding the life-cycle management of computerises systems may be found within the PIC/S Good Practices for Computerised Systems in Regulated GXP Environments.

Investigational medicinal products (Annex 13)

The Australian clinical trial handbook contains guidance on manufacturing products for clinical trials.

Manufacture in Australia

The manufacture of medicines for initial experimental studies in human volunteers (which generally means first-in-human trials, which are generally, but not always, Phase 0 and Phase I trials) is not subject to inspection and licensing by the TGA (specified in item 1, Schedule 7, *Therapeutic Goods Regulations 1990*). However, the Australian manufacture of **all other** clinical trial medicines is subject to inspection (including Annex 13) and licensing by the TGA.

Manufacturers in Australia of investigational medicinal products for clinical trials in phase 3 and phase 2 that are not initial experimental studies in human volunteers must hold a valid TGA licence that **specifically authorises** that site for the manufacture of clinical trial products.

Even if a pilot facility is dedicated for the development of dosage forms and new products, and is not used for the manufacture of saleable product, it is still subject to TGA inspecting and licencing if it is used to manufacture investigational medicinal products for clinical trials that are not initial experimental studies in human volunteers.

Labelling investigational medicines

‘Certain characteristics’ in clause 32 of Annex 13

The ‘certain characteristics’ in clause 32 of Annex 13 of the PIC/S Guide to GMP for medicinal products refers to non-commercial clinical trials performed by researchers without the participation of the pharmaceutical industry. The requirements in this clause relate to the way these products are to be labelled.

Qualification and validation (Annex 15)

For qualification and validation guidance, TGA encourage the use of PIC/S recommendation publications such as:

- PI-006-3 Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation (recommendations)
- PI-007-6 Validation of Aseptic Processes (recommendations)

However, these are **for guidance only** and may not fully reflect the current requirements of PIC/S Guide to GMP.

All equipment used in the manufacture of medicinal products must be appropriately qualified following the principles outlined in Annex 15, section 3. Acceptability of the approach taken will be assessed during inspections on a case-by-case basis.

The nature and extent of qualification should be determined based on risk management principles. Depending on the use, stage in the equipment lifecycle and nature of the equipment, some of the stages outlined in Annex 15 section 3 may be omitted where appropriately justified, based on risk. It is generally expected that all stages would be addressed in the qualification of new and/or complex equipment.

Retrospective process validation no longer permitted

There should be no existing medicines supplied for which appropriate and documented validation is not currently in place. The manufacturing process should be validated **before** the product is placed on the market.

Process validation is a critical step in assuring the quality of medicinal products. When Annex 15 was originally published in 2001 the provision for retrospective validation was given to provide a means by which existing products could be validated.

As the process validation requirements of Annex 15 have been in place for over 15 years, it is now expected that all products currently manufactured are validated, and that new products undergo validation prior to release to the market.

Unfortunately, the previous provisions for retrospective validation could be incorrectly interpreted by manufacturers to suggest that products may be released to market prior to process validation being completed. The changes to Annex 15 rectify this issue.

Any existing validations based on retrospective validation will be accepted; however, any new products, processes, updates or changes to existing processes should undergo full prospective process validation.

Application of concurrent process validation

For registered therapeutic goods, concurrent process validation may only be conducted where there is a strong benefit-risk ratio for the patient, i.e. to permit timely access to a critical medicine.

For medicinal cannabis product dosage forms made available under the Authorised Prescriber scheme, Special Access Scheme (SAS), or clinical trials pathways, concurrent process validation is permitted.

Concurrent process validations should be approved under the site's PQS and where used, the results and conclusion of any supporting data should be made available to the authorised person performing release for supply of the product.

Number of batches used in process validation

The number of batches used for process validation should be determined and justified by the manufacturer based on risk management principles. Our general expectations are that:

- For a new process or product, a minimum of 3 batches are to be conducted for validation purposes.
- For a process subject to technology transfer from one site to another, an extensive evaluation and risk assessment (with supporting data) are to be conducted regarding the similarities and differences in manufacturing processes, equipment, methods and materials should be in place to justify performing less than three batches.
- For changes to existing (validated) processes (e.g. batch size increase), an extensive evaluation and risk assessment (with supporting data) are to be conducted regarding the similarities and differences in manufacturing processes, equipment, methods and materials should be in place to justify the number of batches selected.

Any variations from this approach should be clearly documented and justified by the manufacturer using sound QRM principles.

Batch sizes for process validation

The process must be validated for the smallest and the largest batch sizes intended to be manufactured for commercial use. Process validation may not be required for intermediate batch sizes if it can be demonstrated, based on risk assessment, that process consistency can be achieved for any intermediate batch size.

Scope and extent of validation and risk

The scope and extent of validation should be based on risk according to the manufacturer's quality risk management procedures. Qualification and validation work is required to control the critical aspects of the particular operation and a common sense approach should be applied.

Performance qualification (PQ) and process validation

For significant changes to equipment (e.g. for new or modified items of equipment), the performance qualification is separate from and precedes process validation.

For minor changes not impacting on already qualified equipment (e.g. to processing parameters only):

- performance qualification may be performed in conjunction with operational qualification and process validation
- separate installation qualification and operational qualification are not necessary

TGA guidance developed for the application of quality risk management in the manufacture of listed and complementary medicines (including registered complementary medicines) may assist you with Process validation activities related to manufacture of medicinal cannabis products.

Critical Quality Attributes (CQA) and Critical Control Parameters (CPP)

CQAs and CPPs are important elements of product and process knowledge and should be used in the design, validation and control of manufacturing processes.

A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are used to guide process development and control strategies. The list of potential CQAs can be modified as product knowledge and process understanding increases.

A CPP is a process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

Ongoing process verification (Annex 15 clauses 5.28 - 5.32)

Ongoing process verification is required for all therapeutic goods, irrespective of the method used for process validation.

Ongoing process verification is used periodically to evaluate process parameters and trends and ensure that processes are consistent, and remain in a validated state. The outcomes from the OPV exercise should be used to look at any correlation between process capability and trends identified in the PQR. The frequency of the verification should be based on risk management principles.

Use of materials from approved suppliers for validation

When conducting validation exercises, it is expected that raw materials from approved suppliers are used. However, in exceptional circumstances, materials from unqualified suppliers may be used where supported by a comprehensive risk assessment.

It is expected that this would only apply when concurrent vendor approval is underway, such that the material under evaluation is part of the validation exercise. There must however be an appropriate justification to use the unapproved material based on all of the following:

- the risk to the following manufacturing process, plant and other products
- assurance that the vendor has met the specifications required
- suitable controls regarding approval, analysis and release of the material
- adequate control regarding the starting material issuance and reconciliation
- relevant systems in place to prevent release of the validation batches prior to full qualification of the material

Validation of legacy products

Legacy products are older products that may have been manufactured for a long period of time using well established processes and technologies.

Where these products are transferred from one site to another, it is expected that the product is re-validated in accordance with the marketing authorisation and that, where identified, manufacturing processes should be updated to meet current standards and the necessary modifications to the marketing authorisation made.

The validation requirements for legacy products must meet the current marketing authorisation standards and if required should result in incorporating current validation requirements.

Clear processes should be in place to facilitate the transfer of process knowledge from the originating site. Manufacturers of transferred products should be in possession of appropriate validation and quality documentation from the original site of manufacture, in support of current validated processing parameters.

Transport verification

The basic expectation is that all products (including bulk products, finished products, samples and IMP's) are transported in full accordance with their labelled, authorised and appropriate storage conditions, and that the supply chain has been formally evaluated and confirmed as effective. This assessment should be conducted using sound QRM principles. It is not acceptable to store or transport medicines outside their labelled and approved storage conditions:

- Consideration should be given to the supply chain used for each medicinal product, and the inherent hazards to product quality, e.g. temperature excursions, potential security breaches, and their respective risks.
- Appropriate arrangements should be in place to monitor storage conditions in order to demonstrate continued compliance. The responsibilities for the transportation (including validation), monitoring and storage of medicinal products should be clearly specified within Quality or Technical Agreements.

TGA does not currently inspect the wholesale distribution of therapeutic goods that have been released for supply.

TGA inspections do include an evaluation of the transport conditions for starting materials, bulk and packed medicines between sites of manufacture and clause 1.8 (ix) would apply in these circumstances.

The responsibility for oversight of wholesale of medicines in schedules 2, 3, 4 & 8 of the Poisons Standard currently sits with the states and territories, who may issue relevant permits and licences for wholesalers.

Validation of cleaning processes

Limits for the carryover of product residues

Limits for residue carryover should be based on a toxicological evaluation of the active materials. These evaluations should be verified by a toxicologist (or equivalent) and performed in accordance with current guidance. (Guidance may be found in EMA/CHMP/ CVMP/ SWP/169430/2012 Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities).

Qualified toxicologist

Toxicological limit determinations should be determined by a person with reasonable knowledge/experience of the application of toxicological concerns in determining Health Based Exposure Limits (HBEL) but this person does not have to be a qualified toxicologist.

HBEL should be determined by a person who has adequate expertise and experience in toxicology/pharmacology and pharmaceuticals, as well as experience in the determination of HBEL such as Occupational Exposure Levels (OEL) or Permitted Daily Exposure (PDE). Where experts are contracted to provide the HBEL, contractual agreements in compliance with Chapter 7 requirements should be in place prior to work being conducted.

It is not considered acceptable for manufacturers to 'purchase' HBEL assessments without recording an assessment of the suitability of the provider (including the specific technical expert) as a qualified contractor.

Cleaning validation

Using a dedicated facility and equipment would minimise the risk of contamination with other APIs, this is especially significant in the case of Schedule 8 substances. However, where effective cleaning methods are used and verified through cleaning validation, a non-dedicated facility and equipment may be justified.

There are a number of cleaning validation methods used to verify cleaning effectiveness. Other than visual inspection of the cleaned surface, methods such as water/solvent rinse and swab techniques could be used. Chemical analysis of the rinse and swab extraction would determine the chemical residue level, and swab microbiology testing would determine any microbial residue.

Where cleaning validation studies are conducted using a worst case product or product grouping, there should be a scientific justification that would support such strategies.

Reference and retention samples (Annex 19)

A reference sample is a sample for the purpose of future analysis, which could refer to starting materials, packaging materials or finished products.

A retention sample is a sample representing the batch of finished product as distributed.

Samples from a stability trial program cannot be used as retention samples.

Multipack products and retention samples

Products packaged as complete multipacks do not necessarily need to be kept as retention samples. The requirement is that the amount of retention samples is sufficient to carry out analytical work during the entire shelf life of the product.

Active pharmaceutical ingredient (API – Part II)

The API is the active ingredient that is the starting material for the manufacturing process of the finished product. For medicinal cannabis, the API could be:

- an extracted and purified active component of the cannabis plant (for example a cannabinoid)
- an extract of specified parts of the cannabis plant
- a trituration of specified parts of the cannabis plant
- the dried flower of the cannabis plant separated from leaves and stem

The term 'API starting material' refers to the starting material from which the API is made, not to the API.

The manufacture of the API is required to be in compliance with Part II of the PIC/S Guide to GMP, as well as the relevant parts of the Annexes to the PIC/S Guide to GMP.

If your medicinal cannabis product is being used as an API in clinical trials, compliance with chapter 19 of Part II of the PIC/S Guide to GMP is of particular importance.

GMP does not apply to the cultivation and harvesting of cannabis plants for medicinal use. Table 1 in the introduction chapter of Part II of the PIC/S Guide to GMP provides guidance on the process steps from where GMP is expected to be increasingly applied, depending on the API manufacturing process.

The relevant entries of that table are copied in the table below:

Type of manufacturing	Application of Part II of the Code of GMP to this type of product				
API extracted from plant	Collection of plants	Cutting and initial extraction(s)	Introduction of the API starting material into the process	Isolation and purification	Physical processing and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction(s)		Further extraction	Physical processing and packaging
API consisting of powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting and comminuting			Physical processing and packaging

The blue shading (last three columns of the table) indicates manufacturing steps to which the PIC/S Guide to GMP applies, which means:

- For extracted cannabinoids: GMP does not apply up to cutting and initial extraction but increasingly applies from the introduction of the API starting material into the process onwards.
- For herbal cannabis extracts: GMP does not apply up to cutting and initial extraction but increasingly applies from further extraction onwards.
- For powdered cannabis plant parts: GMP does not apply up to cutting and comminuting but increasingly applies from the moment of physical processing and packaging of the powder onwards.

You may need to seek advice from a GMP consultant or legal advice if you are unclear as to where GMP is required for your manufacturing process.

Some examples to illustrate where GMP starts and licensing is required for API manufacture including Quality Control:

- The processing steps of growing, cultivating, harvesting, cutting and early extraction using CO2 are not considered manufacturing steps **where GMP applies if further processing, such as a purification or decarboxylation step, is performed**. Both an ODC Medicinal Cannabis Licence and Narcotic Manufacture Licence are required for the steps before GMP. If there is no further purification or decarboxylation step performed on the initially extracted cannabis oil, then GMP may apply for the CO2 extraction, dependant on the final use of the material produced.
- The steps of further refinement and/or distillation of the cannabis oil, and concentrating to high percentage (selective cannabinoid i.e. THC), are considered manufacturing steps where GMP does apply and TGO 93 for quality control is required. A Narcotic Manufacture Licence is also required if the cannabinoids (such as THC or CBD) are being isolated.
- A GMP licence to manufacture would be required where GMP applies to the final API processing and packaging.
- In the case where already extracted API was purchased to be refined/undergo further API isolation/refining processes, the extract may be considered as the API starting material; GMP would start for material further processing to the final medicinal cannabis API form and packaging. A GMP licence would be required. An ODC licence would only be required if the API was undergoing refining to isolate cannabinoids such as CBD and THC.
- In the case where a powdered medicinal cannabis API was obtained for further processing to decrease the particle size or packing into final pack. The processing is subject to GMP with a GMP licence required.
- In the case of a medicinal cannabis oil, where GMP didn't apply to its production, was used to manufacture a finished product at a contract manufacturer, the oil would be treated as starting material (API) and would need to be quality control assessed before processing. A GMP licence is required, An ODC licence would only be required if the API was undergoing refining to isolate cannabinoids such as CBD and THC.
- In the case of packaging a medicinal cannabis API at a contract manufacturer, this is considered a GMP step of manufacture. The contract packaging company is required to hold a TGA licence.

- With respect to testing the API to TGO 93 requirements where the manufacturer has no testing capability on site, a contract laboratory may be used provided that the laboratory holds an appropriate TGA licence. The contract laboratory would be required to be GMP licensed for testing of APIs.
- In the case where cultivated medicinal cannabis plant or plant part does not undergo extraction but are comminuted/powdered, dried, packed and released for consumption or to be used as an API, GMP requirements would apply to the powder processing, drying and packing stages. The processes of herb drying and packing would not require a GMP licence if the material is to be used for further production at a GMP licenced manufacturer.
- In the case of a dried and/or milled medicinal cannabis plant (or plant part), where GMP didn't apply to its production, was further processed, extracted or used to manufacture a finished product at a contract manufacturer, the dried and/or milled medicinal cannabis plant (or plant part) would be treated as starting material (API) and would need to be quality control assessed before processing. A GMP licence is required. An ODC licence would only be required if the API was refined, concentrated and isolations occurred.

Cannabis oil and herb manufacture

A Licence to manufacture therapeutic goods (GMP) is required for the manufacture of cannabis oil in Australia unless exempt.

Exemptions may apply in limited circumstances, for example, where the oil extracted from cannabis is used solely as a starting material for medicinal cannabis products by a GMP licenced manufacturer in Australia.

Similarly, this exemption applies to herbs, part of herbs, cut/chopped/dried herbs, the sole therapeutic use of which is as a starting material for medicinal cannabis products for use by a GMP licenced manufacturer in Australia. The exemption does not apply to ground/powdered herbs or herbal substances.

Note that these exemptions do not apply to any requirement to hold a Narcotic Manufacture Licence.

Air quality for crude plants

The environment for drying, crushing and sifting of crude plants should be clean and enclosed but does not need a filtered EU7 air environment.

Air quality for the manufacture of the API

For herbal manufacturing environments, where GMP applies, and during the final stages of manufacture where the API is exposed to the environment, a minimum of EU7 filtered air environment is expected.

The air control system is expected to be monitored and serviced with an appropriate environmental monitoring program.

Storage areas

A separate storage area for crude plants (i.e. unprocessed) should be used, however, if common storage areas are used for crude plants and other materials, including packaging materials, then the manufacturer must be able to justify this practice.

Water quality

The water quality for the manufacture of the API should meet its intended purpose.

Process water used in the early stages of manufacture, unless otherwise justified, it should, at a minimum, meet World Health Organization (WHO) guidelines for drinking (potable) water quality.

Where water used in the process is treated by the manufacturer to achieve a defined quality, i.e. for final stages of API manufacture, the treatment process should be validated and monitored with appropriate action limits. This includes chemical and microbiological limits.

Purified water is expected to be used in the final API manufacturing stage to avoid any chemical and microbial impact on the final API where applicable.

Related guidance and further information

- Final decision on scheduling of cannabis and tetrahydrocannabinols
- Scheduling decision FAQ
- Office of Drug Control – permits and licences to import
- Importing unapproved therapeutic goods and controlled substances

For enquiries about GMP compliance in the manufacture of medicinal cannabis, contact the Manufacturing Quality Branch.

Version history

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